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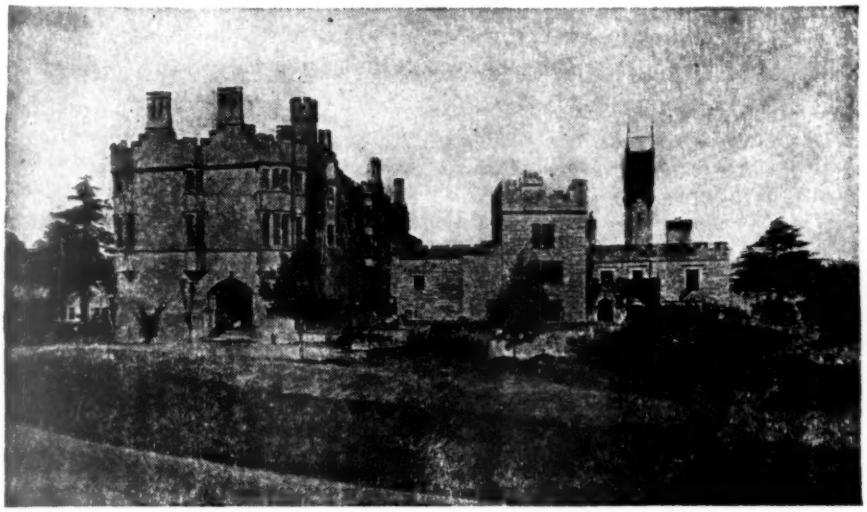

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THE TREATMENT OF RENAL-GLOMERULAR OSTEODYSTROPHY[1]

By C. E. DENT, CHRISTINE M. HARPER, and G. R. PHILPOT

(From the Medical Unit, University College Hospital, London)

With Plates 1 to 7

Review of the current literature dealing with the bone disease associated with chronic renal failure (also known as renal rickets, azotaemic renal osteodystrophy, secondary renal hyperparathyroidism) makes depressing reading, since not only is our treatment for the renal disease itself very unsatisfactory, but there are no consistent claims indicating that anything can be done for the bone disease, which in rare cases is the cause of most of the patient's complaints. The state of affairs is also unsatisfactory on the theoretical level, the various hypotheses proposed to account for the bone disease being unconvincing and controversial.

An early review of several cases was made by Parsons (1927). He classified the 'rachitic' bone changes according to their radiological appearances, which he described as of three types, namely florid, atrophic, and 'woolly'. He was careful to point out that, although all these cases were unresponsive to treatment with vitamin D as then available, cure could occasionally be spontaneous, but only in the atrophic and florid types, and never in the 'woolly' type. Interpretation of these X-rays according to more recent studies (Pugh, 1951; Dent and Hodson, 1954) suggests that the florid types were those which we should consider now to be radiologically indistinguishable from classical rickets. In the 'woolly' type additional changes were present, resembling those seen in hyperparathyroidism. Recent work has also suggested that in rare instances osteosclerosis, paradoxical as this may sound, may occur in addition to, or instead of, the above features of bone disease (Crawford, Dent, Lucas, Martin, and Nassim, 1954). Another early study was made by Graham and Oakley (1938). They treated two patients with 'renal rickets' with alkalis and moderate doses of vitamins A and D. Good healing occurred during a period of one to two years, after which the patients died in uraemia. The first thorough study of the metabolic changes was made by Liu and Chu (1943). They found that the abnormalities of intestinal absorption of calcium and phosphorus could be corrected by dihydrotachysterol in the form of AT10, but not by calciferol. They did not, however, treat any of these patients on a long-term basis with AT10, nor did they claim any favourable clinical results from such therapy. We shall discuss this important study later in the present paper. Further

[1] Received November 5, 1959.

studies of the treatment of the osteodystrophy in renal failure have been reviewed by Albright and Reifenstein (1948). Their report is representative of many others made since that time. They mentioned that it was logical to attempt treatment with either alkalis to correct the acidosis, or with vitamin D to correct the defect of calcium absorption from the gut, or with aluminium hydroxide to lower the raised plasma-phosphorus levels. They gave reasons, however, for preferring to use only alkalis and vitamin D, and of this treatment they said 'as far as the bone disease is concerned the results of the above therapy are most spectacular (unpublished data)'. It is of interest that no details to support this statement were given in their otherwise very well-documented book, nor have we seen any further report along these lines, either from these or from other authors. This makes us wonder whether serious drawbacks could later have arisen in the treatment. The detailed review by de Toni (1955) of the disease for which he favours the term 'classical (or malignant) renal dwarfism' states that 'for the rickets, the usual anti-rachitic treatments, even if given in large doses, show very little response, often none whatever'. Similar views have been expressed by Joiner and Thorne (1953). Stanbury (1957) held the view that, while radiological improvement may be observed in 'azotaemic renal osteodystrophy' after giving vitamin D, this treatment is extremely hazardous except in cases showing mainly rickets or osteomalacia. He emphasized that to give vitamin D to patients mainly showing osteitis fibrosa is 'even with full metabolic control . . . little more than a hazardous therapeutic experiment'.

It was to the especial credit of Albright and his collaborators that they early distinguished a particular form of renal bone disease, usually associated with nephrocalcinosis, which was always amenable to treatment. This was the rickets or osteomalacia associated with 'renal-tubular-insufficiency-without-glomerular-insufficiency'. In such cases the situation was fortunately quite different, and excellent treatment, described in great detail and comprising vitamin D and alkalis, produced complete healing of the bone changes for long periods of time. Stimulated by these studies, several workers have since shown that similar treatment can produce excellent results in other diseases—such as the various forms of the Fanconi syndrome in children and adults, in which, also, the renal tubular damage is out of proportion to the degree of failure of glomerular filtration. The successes obtained in such patients, in whom signs of nitrogen retention and general excretory failure were inconspicuous, served only to stress further the very poor prognosis in the more uraemic patients, for whom we prefer the description used in the title of this paper.

In the present study we describe 13 patients with gross renal-glomerular failure as shown by marked nitrogen retention and diminished urea clearance. These patients were all selected because they showed unambiguous radiological signs of osteodystrophy. One further patient, showing dwarfism without osteodystrophy, is included by way of contrast. In our first patient treatment with alkalis and vitamin D was applied (in 1949) in a rather haphazard fashion. There was some symptomatic improvement for two years, the radiological signs

did not definitely improve, and soon after this time the patient died with uraemia and very gross ectopic calcification. It was difficult to avoid the conclusion that our treatment had worsened his renal condition and had been, perhaps entirely, the cause of the ectopic calcification. We expected that this had been the experience of other workers (note especially the above recent warning by Stanbury (1957)), and for the time being we therefore hesitated to repeat this therapy. When, however, we had learnt more about the actions of vitamin D, and were able to control dosage very carefully in our new Metabolic Ward, we went back to this subject, with our minds again open as to the possible benefit to be obtained by treating such patients with vitamin D or alkalis or aluminium hydroxide. The results of this further study have completely altered our early pessimistic attitude. We hope now to show that the dangers of such therapy, while still present, can be so greatly minimized as to be no longer a sufficient obstacle to its use. Moreover, when the patient survives long enough the bones can be completely healed, with great improvement in symptoms. While a few patients have died suspiciously soon after beginning treatment, the majority have lived much longer than was originally expected on the basis of their first clinical assessment, so that it has not been possible to argue strongly that the treatment is too dangerous to be justifiable. We shall also discuss later the difficult theoretical problems as to the possible mechanism of the osteodystrophy which occurs in chronic renal-glomerular failure, on which some light may have been thrown by these studies.

Methods

The calcium balance studies were all done in our Metabolic Ward, and the general principles laid down by Reifenstein, Albright, and Wells (1945) were used. The patients were given a diet which was maintained unaltered throughout the period of the balance study; but this diet was, in the first instance, composed so as to accord with their own preferences and with our requirement of mineral intake. After six days for equilibration, collections of urine and stools were begun. Carmine markers were used, the stools being bulked and analysed in six-day periods. A complete day's diet was analysed several times during each balance study. All blood samples for chemical analysis were taken at 9 a.m. with the patient fasting (breakfast being delayed), so as to standardize diurnal and other causes of variation. The blood was heparinized and quickly centrifuged, thus avoiding haemolysis, and the plasma was used for analysis. Plasma calcium was determined by the standard macro-method using oxalate precipitation and titration with permanganate.

Throughout this paper we use the term vitamin D to mean either vitamin D_2 (calciferol or ergocalciferol), vitamin D_3 (natural vitamin D or cholecalciferol), or dihydrotachysterol (DHT). By AT10 we mean the proprietary form of irradiated ergosterol, of which 1 ml. is stated to be equivalent to 1·25 mg. of pure dihydrotachysterol. Where we have used pure vitamin D preparations, the compound has been made up in our own Pharmacy in peroxide-free arachis oil with anti-oxidant, and given out in gelatin capsules of various sizes.

Frequent assays have confirmed the stability of our preparations. We have preferred throughout to quote vitamin D dosages on a mg. basis, since in the treatment of hypocalcaemia dosages of all preparations thus expressed are closely comparable. One mg. of vitamin D_2 or $D_3 \equiv 40{,}000$ i.u. Dihydrotachysterol and AT10 have little antirachitic activity in the rat-assay method, so cannot be measured in international units. Throughout this paper the term plasma phosphorus is used to indicate inorganic phosphate measured as phosphorus.

Case Histories

The 14 patients are taken in chronological order of their first attendance at University College Hospital. They comprise a consecutive series selected (except Case 1) only on the basis of the feasibility of admitting them to the Metabolic Ward for detailed study.

Patient	Blood-pressure	Haemoglobin (%)	Plasma Ca (mg./100 ml.)	Plasma P (mg./100 ml.)	Plasma Urea (mg./100 ml.)	Plasma alkaline phosphatase (King–Armstrong units)	Plasma Na (m.-equiv./l.)	Plasma K (m.-equiv./l.)	Plasma Cl (m.-equiv./l.)	Plasma HCO_3 (m.-equiv./l.)	Albumin (g./100 ml.)	Globulin (g./100 ml.)
1. Donald O'S.	116/66	64	10·3	6·3	168	25	..	..	..	17	..	..
2. William B.	152/110	66	6·9	6·0	258	41	..	5·1	..	22	..	..
3. James L.	110/60	69	8·8	6·1	126	62	147	4·6	106	18	..	..
4. Graham P.	90/60	92	9·8	4·3	64	60	145	4·3	111	19	..	..
5. Sheila P.	140/96	75	8·3	5·7	120	109	139	4·0	96	17	4·9	2·8
6. Francis E.	110/70	43	5·6	6·8	172	17	144	4·0	96	11·4	4·7	2·5
7. Guy B.	120/80	60	5·1	8·0	126	22	147	5·2	106	17·9	2·2	2·3
8. Elizabeth F.	120/80	82	7·9	5·4	186	72	144	5·3	101	11·2	4·3	3·0
9. Rose B.	150/100	72	7·2	3·2	120	44	149	4·8	113	20	4·0	1·3
10. Evelyn H.	140/90	74	10·3	10·2	168	23	139	4·5	106	13·7	3·7	2·5
11. Priscilla R.	..	88	9·8	7·4	144	34	143	4·9	..	16·8	4·1	2·1
12. Alfreda W.	130/80	77	8·0	4·3	141	91	142	4·2	109	15·9	3·9	2·2
13. Tony H.	..	87	10·7	5·3	66	26	138	3·5	107	12·7	4·7	2·4
14. Alan B.	135/70	40	6·2	4·6	255	37	146	5·0	106	11·8	4·6	2·2

Case 1. Donald O'S., a schoolboy aged 16, was admitted on 7.11.49, complaining of pains in his hips and difficulty in walking for the last two years. He was known to have had kidney disease since the age of 11, when his urine was examined and found to contain protein after an investigation on account of enuresis. He remained perfectly well for the next three years; he then began to get pain in the lower back, was found to be anaemic (haemoglobin 57 per cent.), and chronic nephritis was diagnosed. The pain did not improve with rest in bed, and during the last five months it had begun to spread to his hips and to cause limping. X-rays had shown an appearance suggesting bilateral slipped epiphyses. This deformity was corrected by skin traction on a Balkan beam. There was nothing else of significance in his personal or family history, nor any previous illness suggesting any form of renal disease. On examination he looked pale and small (height 5 feet). His body proportions were normal. Puberty had occurred. There were no other definite physical signs.

Investigations. X-rays showed marked hyperparathyroid changes, his hip deformity and pain being due to erosions of the femoral necks with some slipping down of the epiphyses. The kidney outlines were very small. Some other investigations are shown in the Table. The urine contained a trace of protein, with numerous pus cells, and occasional red cells and granular casts.

He was given each day 2·5 mg. calciferol, 10 g. calcium gluconate, 5 g. sodium citrate, and 7 g. citric acid. On this treatment his blood-urea level fell from 168 mg. to 96 mg. per 100 ml., and he felt a little better. He was sent home to continue the same treatment, which was maintained for the next 18 months,

the dosage of calciferol remaining at 2·5 mg. daily. He made good symptomatic improvement, the pain in his hips lessening. X-rays, however, showed increasing erosions of the femoral necks and increasing slipping of the femoral epiphyses. Occasional blood tests showed that the serum calcium remained normal during this period, but the urea and phosphorus were slowly increasing. He remained ambulant until a fortnight before his last admission, when he complained of increasing tiredness, weakness, and irritation of the skin. He was still normotensive; there was a rash in the flexures of his elbows, shown on X-ray to contain metastatic calcium deposits, his blood urea was 384 mg. per 100 ml., and he developed pericardial friction. He died 10 days later.

Post mortem he was found to have four large hyperplastic parathyroid glands, and marked ectopic calcification in his arteries; his kidneys were small, and he had megaloureters. A bulge in the posterior wall of the prostatic urethra suggested a possible cause of chronic urinary obstruction. The femoral head was found to be separate from the remaining eroded stump of the femoral neck. On histological section active osteitis fibrosa was found.

Case. 2. William B., a labourer aged 25, was admitted on 21.5.53, complaining of increasing weakness and unsteadiness of his legs for the last year. He gave a history of bladder trouble since birth, having had enuresis till the age of nine, when he was treated in hospital and a diagnosis of nephritis was made. Six years ago he had had acute retention of urine, the reason not being discovered, but he later developed difficulty in emptying his bladder, and a bladder-neck resection was done which relieved it. His difficulty in emptying the bladder recurred a year ago, and he was given a suprapubic cystostomy, which he maintained till the time of admission. Until this was done he had been working full time as a labourer. When his present complaint of weakness of the legs began he was unable to continue working. There was nothing else of note in his personal or family history. On examination he was pale but well-built, with a marked hydrocephalus, Klippel–Feil malformation, kyphoscoliosis, and remarkably long limbs with relation to his trunk. His suprapubic cystostomy was working well. He had a marked foot-drop, with weakness of dorsiflexion; the plantar responses were flexor. There was some hyperaesthesia of lower limbs, with diminished vibration sensation.

Investigations. X-rays showed generalized hyperparathyroid erosions of the bones, with marked osteosclerosis of the vertebral bodies. There was also marked ectopic calcification in the arteries. There were multiple skeletal malformations, including spina bifida and hemivertebrae. Some other investigations are shown in the Table. The urine contained protein 0·5 parts per 1,000 and numerous pus and red cells, and grew a mixed flora.

We concluded that the recent trouble with his legs was of neurological origin, but that in addition he had chronic renal failure, perhaps resulting from a neurological bladder disturbance, and renal osteodystrophy. The calcium balance while he was taking sodium bicarbonate is shown in Fig. 1. Note that there is no substantial difference in calcium metabolism as compared with other patients reported here who were not receiving alkalis. Attempts were made to render the patient's urine sterile, and to deal with his uraemia by diet. Before we could go much further, however, he developed a severe urinary infection resistant to various antibiotics; he slowly became more and more uraemic, and died on 10.8.53.

Post-mortem examination showed chronic cystitis and bilateral hydronephroses and hydroureters, with no urethral obstruction. He had four large hyperplastic parathyroid glands. There were areas of softening in his spinal

cord, and an internal hydrocephalus. It was concluded that the retention of urine was of neurological origin.

This patient was recorded from the radiological point of view as Case 3 of the paper by Crawford, Dent, Lucas, Martin, and Nassim (1954) on renal osteosclerosis.

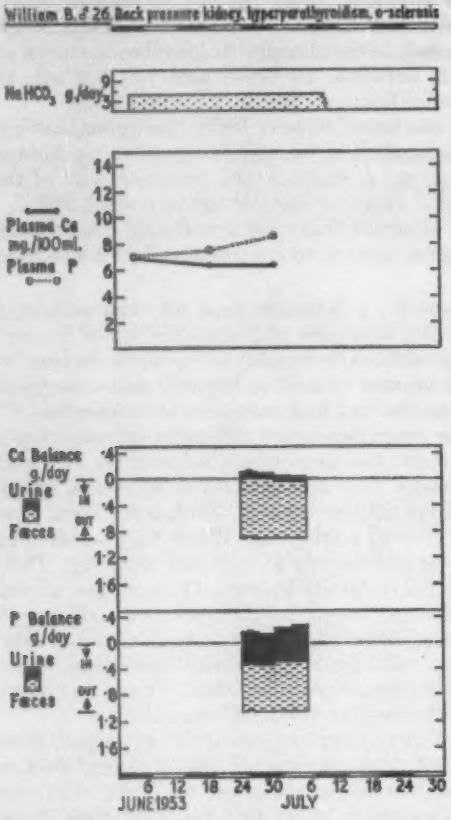

FIG. 1. Metabolic data in Case 2. The balances in this and subsequent figures are drawn according to the standard convention of Albright and Reifenstein (1948).

Case 3. James L., a schoolboy aged 16, was admitted on 23.1.54, complaining of aches and pains in the legs and increasing knock-knee during the last year. The knock-knee came on very rapidly, so that by July 1953 there was a distance of 6 inches between his ankles. He was then admitted to the Oswestry Orthopaedic Hospital (Mr. G. K. Rose), and plasters were applied with wedging, by which his knock-knee was almost straightened. He was later given leg irons for walking. While this was going on rickets was diagnosed and chronic renal damage noted, and he was sent to University College Hospital for further investigation and possible medical treatment.

With regard to his past history he volunteered no particular complaints, having been passed as quite normal on several medical examinations, the last

time when he was aged 14. On questioning, however, his mother agreed that he had always been excessively thirsty. She had also noticed that he was always short as compared with their relatives. There was no further relevant information from his personal or family history. On examination he was short in stature (4 feet 11½ inches), but of normal proportions. He was pale, but

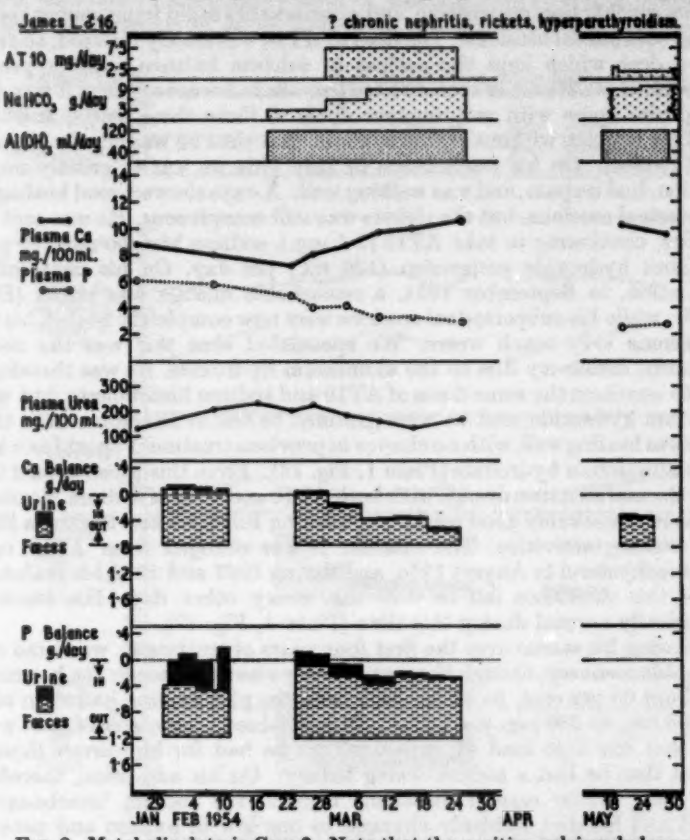

FIG. 2. Metabolic data in Case 3. Note that the positive calcium balance on treatment is about twice the simultaneous phosphorus balance, indicating that new bone formation is taking place.

otherwise healthy-looking and active. He walked with some difficulty using leg irons. There were 3 inches of knock-knee, but otherwise no definite physical signs.

Investigations. X-rays showed gross rickets, with conspicuous early hyperparathyroid erosions of the phalanges (Plate 1, Fig. 14). There was also osteosclerosis, especially marked in the lumbar vertebrae. Renal outlines were seen, and appeared very small. Some further investigations are shown in the Table. The urine contained protein 0·3 parts per 1,000, but was normal on microscopy and sterile.

It was decided that he was suffering from renal-glomerular osteodystrophy due to some cause not yet determined. Medical treatment was decided upon as offering the only hope of improvement. His metabolic data are shown in Fig. 2.

Note, on treatment, the rapid improvement in calcium balance, and its maintenance two months later. It was found that on combined treatment with aluminium hydroxide and sodium bicarbonate no change occurred in the calcium balance. It was decided, therefore, to add large doses of dihydrotachysterol in the form of AT10. On this treatment the calcium and phosphorus balances quickly became positive, and a remarkably rapid improvement occurred in his subperiosteal erosions. The dose of AT10 was slowly reduced, so as to discover a dose which kept the patient in calcium balance without producing hypercalcaemia. He made such an excellent clinical recovery that it was decided to send him home with maintenance doses of these three drugs, and that he should try walking without leg irons. From that time he was closely observed as an out-patient. On his readmission in May 1954 he was in greatly improved condition, had no pain, and was walking well. X-rays showed good healing of the subperiosteal erosions, but the rickets was still conspicuous. He was sent home, as before, continuing to take AT10 (2·5 mg.), sodium bicarbonate (10 g.), and aluminium hydroxide suspension (120 ml.) per day. On his next follow-up examination, in September 1954, a remarkable change was noted (Plate 1, Fig. 15): while his subperiosteal erosions were now completely healed, his rickets had become very much worse. We speculated that this was the result of phosphorus deficiency due to the aluminium hydroxide. He was therefore sent home to continue the same doses of AT10 and sodium bicarbonate, but without aluminium hydroxide, and we were gratified to find in December 1954 that his rickets was healing well, with no change in previous treatment apart from leaving out the aluminium hydroxide (Plate 1, Fig. 16). From this time onward he continued the maintenance dosage with both AT10 and 10 g. of sodium bicarbonate, and was in remarkably good condition, working full time and leading a life with many evening activities. The vitamin D was changed from AT10 to pure dihydrotachysterol in August 1956, and during 1957 and 1958 his maintenance dose of this substance fell to 0·25 mg. every other day. His bones were radiologically normal during this time (Plate 1, Fig. 17).

Reviewing his status over the first four years of treatment, we found a quite remarkable recovery, though there was a very slow decrease in the haemoglobin from about 60 per cent. to 50 per cent., and the plasma urea had risen steadily from 200 mg. to 250 mg. per 100 ml. He remained normotensive, but we were afraid that the high load of sodium might be bad for him, even though we assumed that he had a sodium-losing kidney. On his admission, therefore, in March 1958, under careful metabolic control, the sodium bicarbonate was stopped and his diet suddenly changed to one low in sodium and potassium. We very quickly confirmed the fact that he was unable to retain either of these cations; for his urinary output remained high, and he lost weight very rapidly. Indeed, he became moribund within a week, with a plasma urea of 720 mg. per 100 ml. Active measures were taken to replenish his electrolytes, and he slowly recovered. He was his old self again by May 1958, and from then until April 1959 continued in good condition, working full time and active as usual. By the latter date, however, he was beginning to feel more easily tired and to become oedematous. He then got bronchitis, on recovery from which he was readmitted to University College Hospital on 6.5.59, feeling only a little worse than usual, but greatly oedematous. Soon after admission he had an epileptiform convulsion, which we interpreted as probably due to alkalosis from excessive intake of sodium bicarbonate. The same evening, and before we had taken any blood for analysis, he had another convulsion, after which he died suddenly.

Post mortem he was found to have very small, scarred kidneys, with dilatation of the pelves and upper ureters to a point where there appeared to be, on each

side, a distinct constriction with a small mucosal valve in the lumen. No other abnormality was found in the urinary tract. The parathyroid glands were moderately enlarged (weight 450 mg.).

Case 4. Graham P., a schoolboy aged 13, was admitted on 9.6.54, complaining of an increasing degree of knock-knee over the last two years. He had been

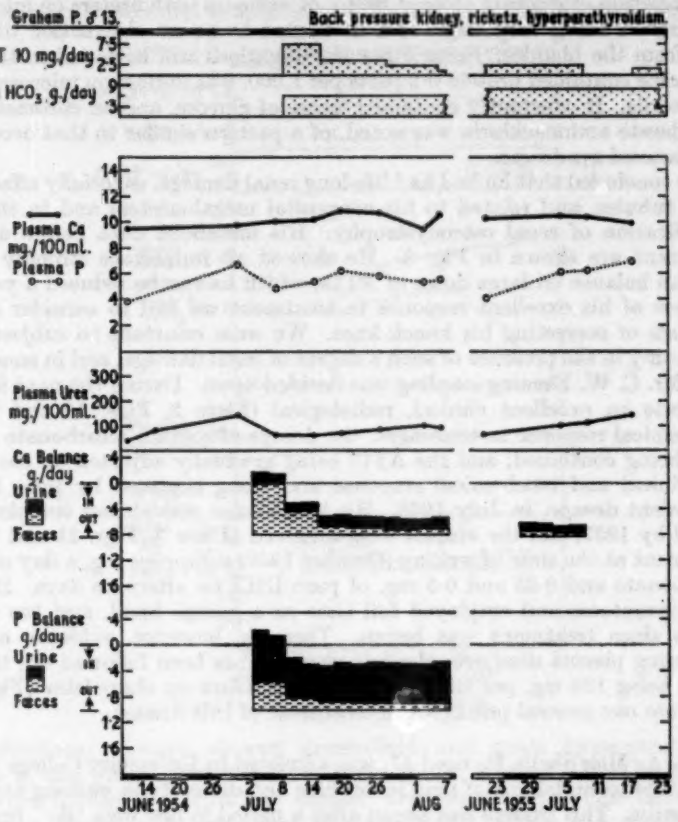

FIG. 3. Metabolic data in Case 4.

treated at first by wedging his heels, but the knock-knee progressed, and more recently his gait had become awkward and he was beginning to feel a dull ache in his knees. He was otherwise well. On questioning him and his mother, however, it was clear that he had been excessively thirsty since he was a child. He had always been much shorter for his age than his three sibs. At the age of 14 months he had had an illness, with vomiting and loss of weight, for which he was admitted to hospital and a diagnosis of 'acidosis' was made. He was treated with diet, and slowly improved. He had no further feeding problem after the age of four years. There was nothing else relevant in his personal or family history.

On examination he was a small (height 4 feet 7½ inches), rather pale boy of

normal proportions. There was a gross knock-knee deformity, with 8¾ inches between the medial malleoli. The shafts of his long bones were straight. There was a notch across both upper central incisors, which we thought might have been due to defective tooth formation at the time of his original 'acidosis'. He was cheerful and active. There were no other physical signs of note.

Investigations. X-rays showed a florid rickets of recent origin, with also mild hyperparathyroid changes (Plate 2, Fig. 18). Renal outlines were not seen. An excretion cystogram showed reflux of urine up both ureters on micturition, the ureters being very large. There seemed to be no obstruction of urinary flow from the bladder. Some other investigations will be found in the Table. The urine contained protein 0·2 parts per 1,000, was normal on microscopy, and was sterile. It constantly contained traces of glucose, and on chromatography a moderate aminoaciduria was noted, of a pattern similar to that occurring in the Fanconi syndrome.

We concluded that he had had life-long renal damage, especially affecting the renal tubules, and related to his congenital megaloureters and to the recent complication of renal osteodystrophy. His metabolic data before and after treatment are shown in Fig. 3. He showed an immediate strongly positive calcium balance on large doses of AT10, which had to be reduced a year later. In view of his excellent response to treatment we had to consider seriously methods of correcting his knock-knee. We were reluctant to subject him to osteotomy in the presence of such a degree of renal damage, and in consultation with Mr. C. W. Fleming stapling was decided upon. During the next few years he made an excellent clinical, radiological (Plate 2, Figs. 19 and 20), and biochemical response to treatment, the dosage of sodium bicarbonate (8 g. per day) being continued, and the AT10 being gradually adjusted on the basis of his clinical and biochemical response and being replaced by pure DHT, in equivalent dosage, in July 1956. His knock-knee was almost completely corrected by 1957, and the staples were removed (Plate 3, Figs. 21 and 22). His treatment at the time of writing (October 1959) comprises 8 g. a day of sodium bicarbonate and 0·25 and 0·5 mg. of pure DHT on alternate days. He is free from symptoms and employed full time as a garage hand, and has grown 8 inches since treatment was begun. There is, however, evidence of slowly increasing plasma urea over the five years he has been followed up, the latest figure being 120 mg. per 100 ml. We use his follow-up chart later (Fig. 13) to illustrate our general principles in treatment of this disease.

Case 5. Miss Sheila P., aged 17, was admitted to University College Hospital on 19.9.54, complaining of pain in her hips and difficulty in walking for the last 18 months. This trouble had begun after a period in bed with 'flu', first in the right leg and later in both. It was felt from the hip down the thigh to the upper part of the lower leg, was 'like toothache', and was worse when weight-bearing. It had recently become so bad as to prevent her from walking. She was otherwise reasonably well in general health. Her past history was very relevant to the present complaint. At the age of two years she had been admitted to hospital with fever, vomiting, and a swollen face, with intermittent haematuria. At that time her blood-pressure was 120/70, and the blood urea 58 mg. per 100 ml. with a clearance of 43 per cent. A trace of protein remained in the urine after her recovery from this episode. She had another illness, with swelling of the face, at the age of five years. At the age of 10 she was readmitted to hospital with further swelling of her face and haematuria, and from then until the present time she had been treated with a low-protein, low-salt diet, and had had intermittent oedema. During the last three years her parents had noticed that she

had stopped growing. There was nothing else relevant in her personal and family history.

On examination her main problem was concerned with pain and limitation of movement of the hips, and inability to bear weight on them. She was small for her age, and had no signs of puberty. Her face showed prominent malar bones and exophthalmos. Her gums showed bony hypertrophy. She was pale, but in a reasonable state of nutrition, with no signs of previous rickets. She walked only with pain and difficulty, and then with a marked waddling gait.

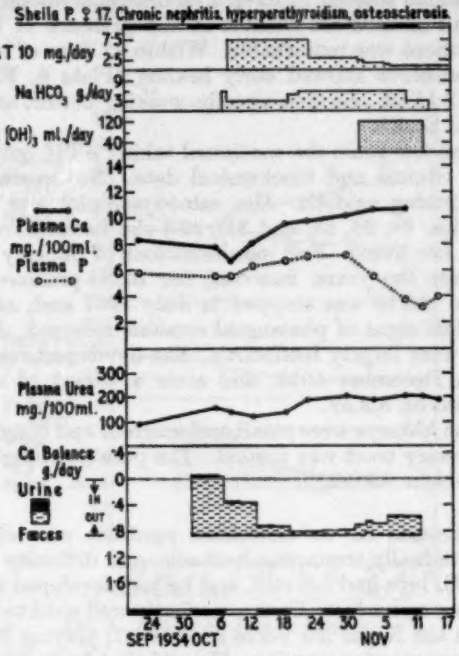

FIG. 4. Metabolic data in Case 5.

Investigations. X-rays showed generalized and gross hyperparathyroid changes in the bones (Plates 4 to 6, Figs. 23, 25, 27, and 29). The femoral necks were fractured and largely eroded, accounting readily for her recent symptoms. Rachitic changes were relatively mild. There was considerable generalized osteosclerosis. The skull was thickened, this change extending to the maxilla and alveolar bone. In consequence her orbits were small, and the cause of her exophthalmos, prominent malar bones, and hypertrophied gums seemed clear. Some other investigations are shown in the Table. The urine contained protein 0·7 parts per 1,000, and was normal on microscopy and sterile.

We concluded that she had chronic nephritis, probably dating from an attack of acute nephritis at two years of age, and that she now had renal osteodystrophy, predominantly of hyperparathyroid type, as the cause of her recent additional complaints. We thought that the mild hypertension worsened her prognosis for life, but that it was still worth while considering medical treatment for the bone disease, which was responsible for her main symptoms.

Her metabolic data and response to treatment are shown in Fig. 4. On a very

large dose of AT10 the calcium balance rapidly became positive, and was well maintained when the dose was greatly reduced. The plasma-phosphorus level showed a large fall in response to aluminium hydroxide. After the control period we gave the patient sodium bicarbonate, in an attempt to assess its value as sole treatment. In the evening of the day it was started she developed severe tetany, with hypocalcaemia. We therefore began AT10, and temporarily lowered the dose of alkali. After a short period with aluminium hydroxide she was sent home receiving AT10 only, the other drugs being stopped, since aluminium hydroxide seemed to have a rachitogenic action (see Case 3) and a large sodium load seemed inadvisable in the presence of hypertension. Her response to treatment was remarkable. Within 22 days of beginning the AT10 her phalangeal erosions showed early healing (Plate 6, Fig. 30). When she went home on 17.11.54, she was already walking better, and was greatly improved in general health.

During the next few years she continued taking AT10 only, in doses reduced as indicated by clinical and biochemical data. No measures were taken to correct her continuing acidosis. Her osteodystrophy was completely healed (Plates 4 to 6, Figs. 24, 26, 28, and 31), and she became free from symptoms and able to earn her living. Full manifestations of puberty developed rapidly during 1955. Over the years, however, her blood-pressure and plasma-urea level slowly rose. AT10 was stopped in July 1957 and, after this, mild but definite radiological signs of phalangeal erosions recurred. Hypotensive drugs were given, but were largely ineffective. She developed retinal haemorrhages and exudates in December 1958, and after a period of increasing uraemic symptoms she died on 8.3.59.

Post mortem the kidneys were small and scarred, and consistent with chronic nephritis; the urinary tract was normal. The parathyroid glands were slightly enlarged (total weight 850 mg.).

Case 6. Mr. Francis E., an electrician aged 32, was admitted on 16.1.55 complaining of gradually worsening backache and difficulty in walking for the last two years. His hips had felt stiff, and he had developed a marked waddling gait and felt unsure on his feet. He was perfectly well until two years previously. He had served in the Royal Air Force in 1943–47, playing Rugby football and taking part in cross-country running. He said that he had been refused for life insurance in 1947 as there was something wrong with his kidneys, but would admit to no urinary difficulties. His parents, however, mentioned that he had always been very thirsty, and was a persistent bed-wetter in childhood and until he joined the Royal Air Force in 1943. He had also had further bed-wetting four years before his admission. There was nothing further in his personal or family history. On examination he was 5 feet 1 inch in height; he had normal body proportions, and was plump and muscular, but rather pale. He walked with a pronounced waddle. There were no other physical signs.

Investigations. X-rays showed a generalized osteosclerosis of the skeleton, suggesting a diagnosis of 'marble bones' disease. His lumbar vertebrae were slightly biconcave, and he had a Looser zone in the middle of one femur. Some other investigations are shown in the Table. His urine contained a trace of protein, but was normal on microscopy and sterile. His metabolic data before and after treatment with AT10 are shown in Fig. 5. Coincident with the positive calcium balance on treatment with AT10 there was an increase to normal of plasma calcium, and both plasma phosphorus and urea decreased, suggesting a marked improvement in renal function. At the same time the calcium balance became positive.

He made an excellent clinical recovery, losing all his pain and being able to walk again quite normally. He went back to work, and continued maintenance treatment with AT10, and later with DHT, but with no attempt to correct his acidosis. In November 1957 he began to feel weak and sick. Up to this time he had shown a rising plasma-urea level and increasing anaemia, which worsened steadily until he died in uraemia, having remained normotensive, on

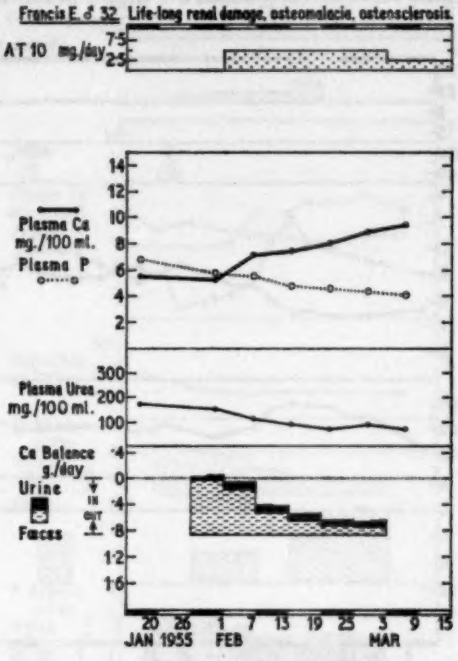

FIG. 5. Metabolic data in Case 6.

7.2.58. *Post mortem* his kidneys were small, and contained many cysts, suggesting chronic pyelonephritis. The urinary tract was normal. Only two normal-sized parathyroid glands could be found. His bones showed marked osteosclerosis.

Case 7. Guy B., aged nine and a half years, was admitted on 3.9.55, complaining of increasing knock-knee, difficulty in walking, and pains in his legs during the last year. His previous history was well documented owing to his repeated admissions to other hospitals, and was relevant to his recent complaint. His illness began at the age of two years, when after a febrile attack he developed generalized oedema. At this time he showed the full nephrotic syndrome, but had macroscopic haematuria and a blood-urea level of 53 mg./100 ml. Oedema had continued until a few years ago, when it disappeared. This change coincided with a slow increase of the blood urea. He was normotensive during this time, and was in moderate health apart from being very small in stature. During the last two years X-ray evidence of rickets had been noted for the first time, and had rapidly increased in severity. There was nothing else relevant in his personal or family history. On examination he was very small (height 3 feet 11

inches, weight 21 kg.), but with normal body proportions; he was pale, but quite lively in his behaviour. His fundi showed marked papilloedema, but no other changes. He had 3½ inches of knock-knee, with marked enlargement of the epiphyses of the wrists, knees, and ankles. The long bones were straight.

Investigations. X-rays showed florid rickets of recent origin, with some generalized osteoporosis (Plate 6, Fig. 32). There were no signs of hyperparathyroidism. Some other investigations are shown in the Table. His plasma

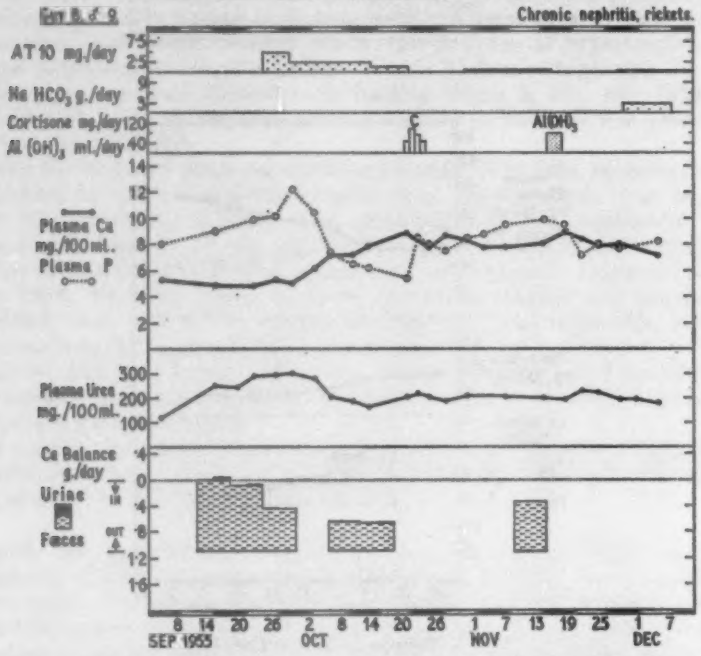

FIG. 6. Metabolic data in Case 7. Note the very low urine-calcium level here, which in most cases was too small to be shown on the charts. The initial increase in plasma urea was probably the result of higher protein intake in hospital.

cholesterol was 685 mg. per 100 ml. There was gross proteinuria, mainly comprising albumin, and there were also heavy traces of glucose and a moderately increased output of amino acids.

His metabolic data before and after treatment with DHT are shown in Fig. 6. Note that, as in Case 6, there was a marked tendency for plasma calcium and phosphorus levels to rise and fall in opposite directions. The improvement in his calcium balance coincided with a marked improvement in his X-rays. He lost the pain in his legs, and became able to walk and move about much more easily. An interesting feature of this period of treatment in hospital was that he showed clear signs of vitamin-D intoxication on the three occasions on which his plasma calcium increased to just over 9·0 mg. per 100 ml. We were a little slow to realize on the first occasion that this indicated a pathological increase of calcium in view of his very low plasma-protein level. (Our rough working rule is that a reduction of 1 g. plasma protein per 100 ml. lowers the normal total plasma calcium by 1 mg. per 100 ml.) He was given a short course of

cortisone on the first occasion. A small decrease in plasma calcium followed, with marked symptomatic improvement. When the cortisone was stopped a rebound phenomenon seemed to occur.

After he had gone home, with maintenance doses of DHT, he continued to improve and became free from symptoms for a while. We were especially

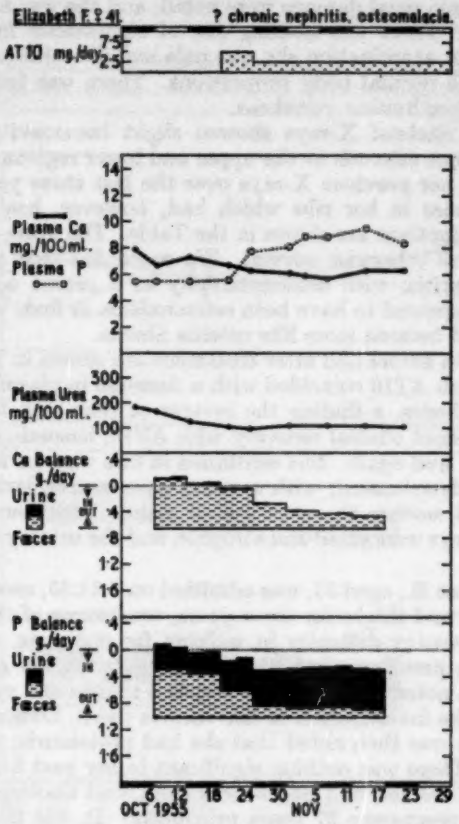

FIG. 7. Metabolic data in Case 8. Separate charting of the plasma phosphorus level and urine phosphorus output showed that there was no change in renal threshold during the treatment by AT10.

interested in the rapid healing of his rickets (Plate 6, Fig. 33), the sole treatment being a drug (DHT) generally supposed to have no antirachitic action. The plasma urea, however, continued to increase, and the patient slowly developed uraemic symptoms, and died on 12.2.56. *Post mortem* both kidneys were small and scarred; the urinary tract was normal. Three normal-sized parathyroid glands were found.

Case 8. Mrs. Elizabeth F., a housewife aged 41, was admitted on 5.12.55, complaining of a severe pain in the lower back and down both thighs, with increasing difficulty of walking, both of which had come on during the last year.

She had also felt considerable weakness in her legs, and had developed a pronounced waddling gait. The pain and weakness was severe enough to prevent her from walking more than a few paces at a time. She had been known to have kidney disease since 1935, when she had pyelitis in her first pregnancy. She had further attacks of pyelitis in 1937 and 1948. In 1952 anaemia and chronic renal damage were noted, and she was also suffering from pains in her ribs. There was nothing else of significance in her personal or family history. On examination she was pale and ill looking, her height being 5 feet 1 inch, with normal body proportions. There was tenderness over the lower ribs and upper lumbar vertebrae.

Investigations. Skeletal X-rays showed slight biconcavity of the lumbar vertebrae, with some sclerosis at the upper and lower regions of each vertebral body. Review of her previous X-rays over the last three years showed some typical Looser zones in her ribs which had, however, healed subsequently. Some other investigations are shown in the Table. The urine contained a trace of protein, but was otherwise normal. We concluded that she probably had chronic pyelonephritis, with osteodystrophy as a recent complication. The latter condition appeared to have been osteomalacia at first, which then healed spontaneously and became more like osteitis fibrosa.

Her balance data before and after treatment are shown in Fig. 7. Note here that treatment with AT10 coincided with a decrease in plasma calcium and an increase in phosphorus, a finding the reverse of that seen in Cases 6 and 7. She made an excellent clinical recovery with AT10, becoming free from symptoms and walking well again. She continued in this way for about six months, and then slowly deteriorated, with a rising plasma-urea level, until she died on 19.10.56. *Post mortem* the parathyroid glands were found to be slightly enlarged, the kidneys were small and atrophic, and the urinary tract was normal.

Case 9. Mrs. Rose B., aged 52, was admitted on 5.12.55, complaining of pains in the lower back and thighs for three years, tenderness of the ribs and arms for one year, increasing difficulty in walking for one year, and lassitude for three years. On a previous admission elsewhere during her earlier symptoms, anaemia had been noted which did not respond to iron and vitamin B_{12}. More recently, during the investigation of her various pains, Looser zones were seen on her X-rays. It was then noted that she had proteinuria, and that she was mildly uraemic. There was nothing significant in her past history except that she had been told she had had rickets as a child, and that she had had kidney trouble during a pregnancy 27 years previously. It was not possible to get further details. On examination she was frail and pale, her height being 4 feet 11½ inches, with normal body proportions. She had generalized bony tenderness, and walked with a waddling gait.

Investigations. X-rays showed typical Looser zones in the pelvis and early hyperparathyroid changes in the phalanges. Some other investigations are shown in the Table. The urine contained protein 0·7 parts per 1,000, was normal on microscopy, and was sterile. We concluded that she had long-standing renal damage of unknown origin, which was now manifested as anaemia and an osteodystrophy mainly comprising osteomalacia.

The balance results before and after treatment are shown in Fig. 8. Note that her calcium balance was slower to respond to treatment than in our earlier cases, owing to our preferring now to use a smaller initial dose of vitamin D. Her plasma calcium and phosphorus levels also moved in opposite directions, under the influence of vitamin D on the first occasion and of an increase of dietary calcium on the second. She made an excellent clinical recovery,

becoming quite free from pain and able to return to work. During follow-up observation, however, there was a slow and steady rise in the plasma-urea level, and a decrease in haemoglobin. Her bone pains were fully controlled, and X-rays showed complete healing. She remained normotensive. She died in uraemia on 23.5.57. There was no post-mortem examination.

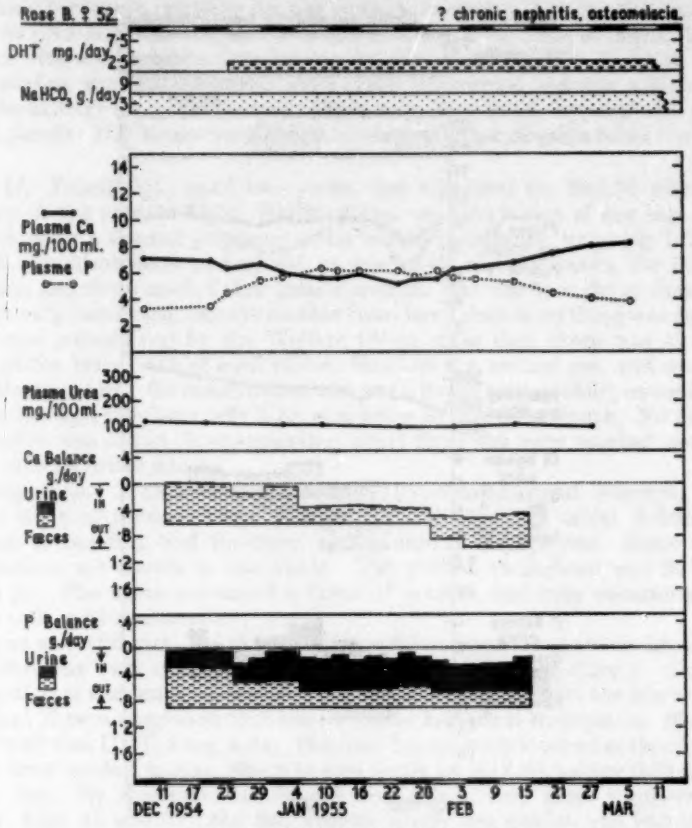

FIG. 8. Metabolic data in Case 9.

Case 10. Mrs. Evelyn H., a housewife aged 46, was admitted on 7.8.56, complaining of increasing low back pain and pains in the legs for the last two years, with a waddling gait for one year, and more generalized pains in the arms during the last six weeks. She had recently become so weak as to be unable to walk. She had had pyelitis during her third pregnancy 17 years ago, and an admission to a mental hospital for a nervous breakdown 10 years ago. There was nothing else of note in her personal or family history. On examination she looked pale, but was well-nourished. All her terminal phalanges except those of her ring fingers were collapsed, producing an appearance of clubbing. She was short in stature (4 feet 10 inches), but of normal body proportions. There were no other bony deformities, and no bone tenderness. No other physical signs were noted.

Investigations. Bone X-rays showed gross generalized hyperparathyroid

erosions. Most of the terminal phalanges were fractured, and there was irregular widening of the sacro-iliac joints and symphysis pubis. In addition generalized arterial calcification was present, and in various sites masses of calcium deposition were seen in the tissues. The kidney shadows were small. Some other investigations are shown in the Table. The urine contained protein 0·3 parts

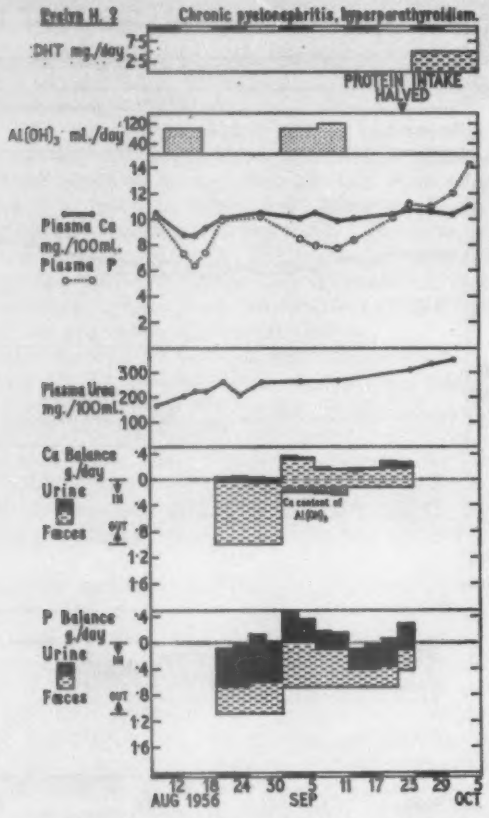

FIG. 9. Metabolic data in Case 10. Owing to the patient's clinical deterioration we were unable to continue the balances when treatment by DHT was begun.

per 1,000, showed numerous pus and a few red cells on microscopy, and grew *E. coli* on culture.

We concluded that she had long-standing renal damage, probably as the result of chronic infection, with the more recent development of an osteodystrophy of mainly hyperparathyroid type. The ectopic calcification, with the high calcium and phosphorus product in the plasma, made treatment by the usual means which produce a positive calcium balance seem unduly hazardous. We therefore attempted to treat her with vitamin D, while giving a low-calcium diet, and aluminium hydroxide to promote phosphorus depletion. We hoped in this way to replenish her bones at the expense of her ectopic calcium deposits.

The metabolic data obtained are shown in Fig. 9. Note especially that there was no 'reciprocation' (see Discussion) of calcium and phosphorus levels in the plasma under the conditions induced. Note also that in the control period the patient was in approximate calcium and phosphorus balance, strongly suggesting that the ectopic calcium came from her bones and not from her diet. The balances became negative on our dietary measures, but by the time we started to give DHT she began to vomit, and balances became impossible to continue. She continued to deteriorate, and died in uraemia on 16.10.56.

Post mortem she was found to have small contracted kidneys with many cysts; the urinary tract was normal. There were four large, hyperplastic parathyroid glands. Her bones were soft, and showed generalized osteitis fibrosa.

Case 11. Priscilla R., aged two years, was admitted on 19.9.56 after the discovery in the routine Child Welfare Clinic of deformities of her legs. She was born, after a normal pregnancy, one month premature, weighing 1·36 kg. She had two admissions to hospital, at one week and six weeks, for feeding difficulties, and there made a slow gain in weight. She was thought at that time to be mentally backward, but the mother considered that everything was normal until it was pointed out by the Welfare Clinic nurse that there was anterior bowing at the lower ends of both tibiae. She had not walked yet, and was still very difficult to feed. On examination she was a lively, plump child, exceedingly small for her age, weighing only 7 kg. and being 27 inches in length. No further abnormality was found on examination apart from the very marked anterior bowing of both lower tibiae.

Investigations. X-rays showed marked hyperparathyroid changes, with minimal signs of rickets (Plate 7, Figs. 34 and 36). The tibial deformities were due to bending and fractures of the eroded metaphyses. Some other investigations are shown in the Table. The plasma cholesterol was 253 mg. per 100 ml. The urine contained a trace of protein, but only occasional pus and red cells, and was sterile.

She was a fretful girl, and it was not possible to perform balance investigations. She was very difficult to feed, and was excessively thirsty. Further investigation of her renal tract was not considered justified, but the history and abdominal X-rays suggested that she probably had renal hypoplasia. She was treated with oral DHT, 2 mg. a day, this dose being slowly lowered as the plasma-calcium level tended to rise. She was sent home on 9.12.56, taking 0·25 mg. of DHT a day. By this time her X-rays had shown very great improvement (Plate 7, Figs. 35 and 37), she had become much less fretful, and had gained 1·5 kg. in weight and 1½ inch in length. She was beginning to walk well, and was less difficult to feed, but remained very thirsty. She was followed up as an out-patient, receiving the same dosage of DHT, until 18.3.57, progress remaining exceedingly satisfactory. She was by then running and walking well. Unfortunately since that date she has failed to attend the hospital, and we have no further news of her.

Case 12. Mrs. Alfreda W., aged 41, was admitted on 2.3.57. She had had no complaints until one year before, when after a minor fall she was found to have broken her upper humerus through a large cystic area. The fracture healed well, but was followed by a similar incident on the other side. At about the same time she began to feel weakness in her knees, which interfered with climbing stairs. She had also been having pain in her chest. On questioning she said she was very thirsty, and had been thirsty since childhood. She was the smallest member of her family, and had had four pregnancies, nine, seven, six, and three

years ago. She was told that she had kidney trouble during the last pregnancy. There was no family history of dwarfism or bone disease. On examination she was a small, pale woman, 4 feet 8 inches in height, and of normal proportions. All fingers except the fourth on both hands showed shortening of the terminal phalanx, which produced a superficial appearance of clubbing. There were no signs of rickets in childhood. Some bone tenderness was present over the lower ribs. Her body build was remarkably similar to that of the adult patient with

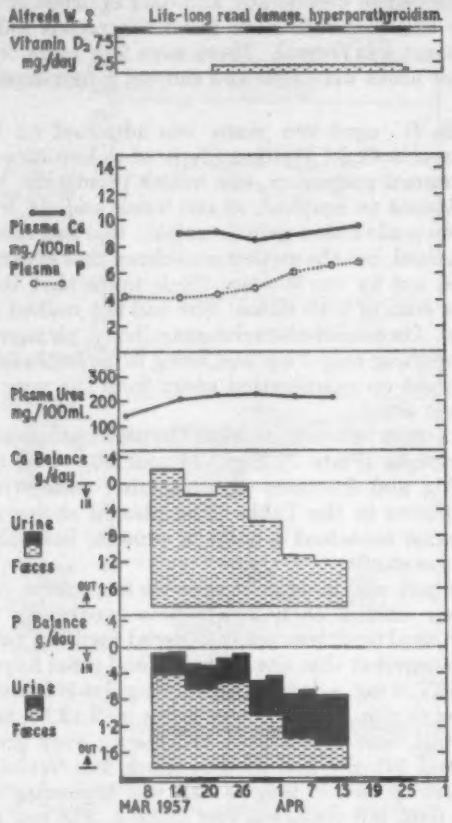

FIG. 10. Metabolic data in Case 12.

coeliac disease and osteodystrophy described as Case 2 by Davies, Dent, and Willcox (1956).

Investigations. X-rays showed gross hyperparathyroid changes in her bones, the collapsed terminal phalanges being due to subperiosteal erosions. There were also patchy cystic appearances in the pelvis and long bones. Some other investigations are shown in the Table. The urine contained protein 0·6 parts per 1,000, but was normal on microscopy and sterile.

We concluded that she had had life-long renal damage, probably due to congenital hypoplasia, which had only worsened comparatively recently. It is of interest to recall that cystic osteitis fibrosa is rare in renal disease, but it can occur in our opinion in cases such as this, in which the history is very long.

The metabolic data before and after treatment are shown in Fig. 10. The results during treatment with vitamin D are broadly similar to those obtained in our earlier cases, in which AT10 or DHT was given. The patient made a good clinical improvement, coinciding with the change of calcium balance on giving vitamin D. We sent her home greatly improved, free from pain, and able to go up and down stairs almost normally. In the follow-up period we have maintained her on reduced doses of vitamin D, and she has made a perfect clinical and radiological recovery as far as her bones are concerned. She is

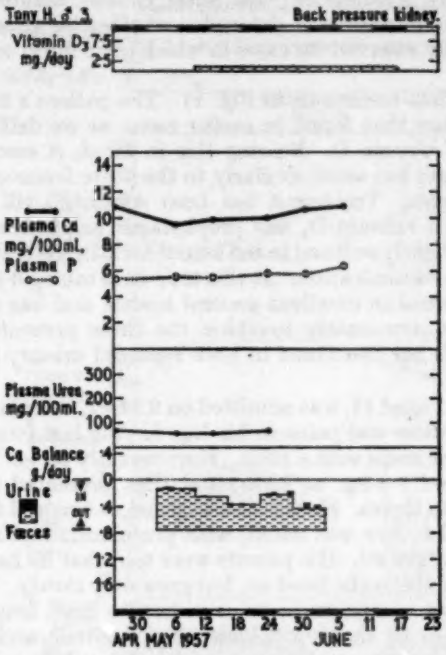

FIG. 11. Metabolic data in Case 13. The collections of urine here were, for technical reasons, 24-hour specimens, not our usual three-day collections.

now able to do all her housework and feels very well, but is still thirsty. There has been a slow increase in her plasma urea to 177 mg. per 100 ml. at the time of writing (October 1959).

Case 13. Tony H., aged three years, was admitted on 23.4.57 for further investigation of his renal status and dwarfism. He had had a normal delivery and weighed 3·8 kg. at birth. Soon after birth he was thirsty, vomited frequently, and failed to thrive. He had a laparotomy for suspected pyloric stenosis which was not, however, confirmed. At six months the blood urea was found to be 135 mg. per 100 ml. Chronic urinary infection was also noted, and subsequently obstruction at the bladder neck and bilateral dilated ureters. A resection was carried out, with further general improvement in his health and a fall of the blood-urea level to 60 mg. per 100 ml. He did well, but remained thirsty and grew slowly. There was nothing further in his family or personal history. On

examination he was a lively, healthy-looking boy, but well below the three percentile for height and weight (height 2 feet 9¾ inches, weight 13·3 kg.). He was normally proportioned, and had no skeletal deformities. He walked well, and was of normal intelligence.

Investigations. Skeletal X-rays showed Harris lines, but no specific signs of metabolic bone disease. Some other investigations are shown in the Table. The urine contained a trace of protein and many pus cells, and grew *E. coli* on culture. We concluded that his renal damage, due to the early urinary obstruction, was probably irreversible. Its main clinical manifestation now was dwarfism. We were interested to determine whether his growth would respond to treatment usually reserved for cases in which more florid osteodystrophy was present.

The metabolic data are shown in Fig. 11. The patient's balance response is less spectacular than that found in earlier cases, as we deliberately gave him a smaller dose of vitamin D. Bearing this in mind, it seems likely that the vitamin D_3 used here has acted similarly to the other forms of vitamin D given to the other patients. Treatment has been continued till the present date (October 1959) with vitamin D_3 and prophylactic sulphadimidine, the dose of vitamin D_3 being slightly reduced to the amount which the child can just tolerate without any signs of intoxication. At this time he is taking 0·25 mg. every other day. He has remained in excellent general health, and has grown faster than normal, his height now nearly touching the three percentile. Bone X-rays remain normal. He has continued to have repeated urinary infections.

Case 14. Alan B., aged 17, was admitted on 9.11.57, complaining of increasing knock-knee deformities and pains in his legs for the last four years. He could now walk only a few steps with a stick. More recently all his bones had become tender. He weighed 1·8 kg. at birth, and then presented feeding difficulty, thirst, and failure to thrive. He was investigated at two and three years of age, when chronic renal failure was noted, with proteinuria and a blood-urea level of about 80 mg. per 100 ml. His parents were told that he had only one or two years to live. Nevertheless he lived on, but grew only slowly. He went to school from six to 13 years of age, and was considered a good long-distance runner. From the latter age he developed increasing lassitude and pallor, with the complaints recorded above, and became an invalid at home. Early rickets was diagnosed radiologically at 13 years, and became florid at 16 years. There was nothing relevant in the family history. On examination he was a very small (weight 23·0 kg., height 4 feet 1½ inches), thin, but quite lively boy, with his trunk a little short for his limbs. He had large ears, and was prepuberal. He was very pale. His heart had a marked systolic thrust, with a generalized systolic murmur. He had general muscular weakness, and his legs showed gross knock-knee, but the shafts of all the long bones were straight.

Investigations. X-rays showed gross rickets, with a trefoil pelvis and a Looser zone in a pubic ramus, florid hyperparathyroid erosions of phalanges, and minimal osteosclerosis of vertebral bodies. Kidney outlines were not seen. Other investigations are shown in the Table. His urine contained 0·1 per cent. of protein, but was normal on microscopy and sterile.

We concluded that he had had primary renal disease, probably agenesis, with at first dwarfism and later rickets (turning into osteomalacia) and secondary hyperparathyroidism as its bony manifestations. He was clearly in a state of terminal uraemia, but it was hoped that treatment would ensure a return to moderate well-being for the short time remaining.

His balance chart (Fig. 12) shows the metabolic state and early response to

treatment. The plasma levels show an interesting reciprocation of calcium and phosphorus levels, due to the changes in dietary intake during a time when the action of vitamin D was manifest. The trial period on sodium bicarbonate corrected his acidosis, the blood pH rising from 7·15 to 7·35 and bicarbonate from 12·5 to 23 m-equiv. per litre, but no effect on symptoms or on calcium and phosphorus metabolism was noted. Note the slow action of vitamin D_3. He made an excellent clinical response, bone pains greatly lessening, and was sent

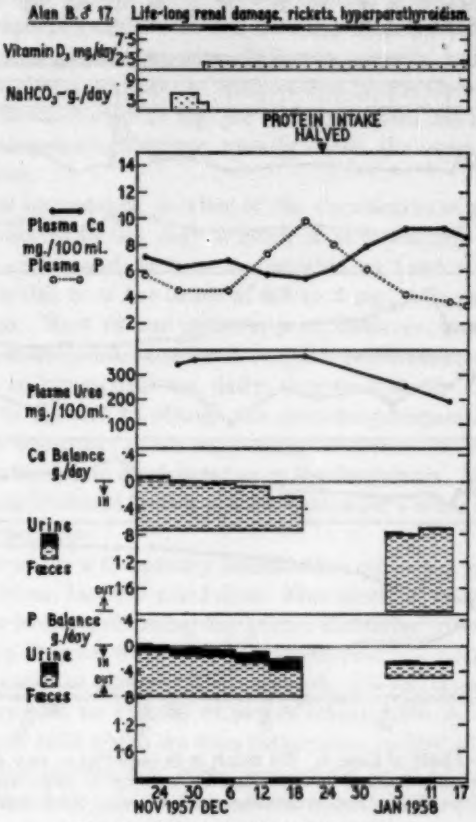

FIG. 12. Metabolic data in Case 14.

home on 19.1.58, with instructions to take a low-protein diet and 2 mg. of vitamin D_3 with 4 g. of calcium phosphate powder daily. He soon became normally active again, climbing trees and going for long cycle rides; by June 1958 the plasma phosphatase had become normal, and the radiological evidence of rickets and parathyroid changes had almost disappeared. In July 1958 an error of judgment was made, for he was sent away for two months with a continuance of the same dose of vitamin D_3 when a blood test showed a plasma-calcium level of 10·0 mg. per 100 ml., which was high in view of his diminished plasma proteins. In September 1958 the plasma calcium was 10·6 mg. per 100 ml., and corneal calcification was visible; his dose of vitamin D_3 was therefore halved, and in the next month stopped altogether. By this time he was

beginning to feel much more easily tired and to vomit occasionally, and his blood-pressure began to rise. He remained moderately active till the end of January 1959, when increasing uraemia and anaemia confined him to bed. He died at home on 22.3.59. There was no post-mortem examination.

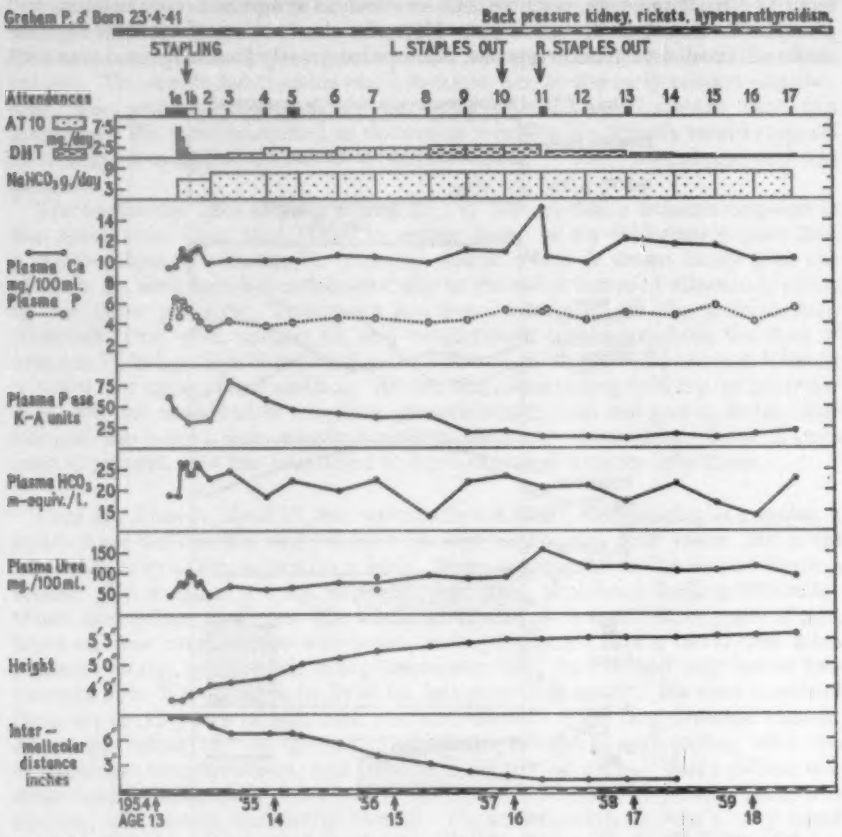

FIG. 13. Follow-up chart of Case 4. We think it is essential in any patient followed up for more than a few months that such a chart be kept up to date. Only in this way can incipient under- and overdosage with vitamin D be detected.

Illustrative Scheme of Medical Follow-up (Case 4)

The chart (Fig. 13) is kept up to date during the patient's repeated attendances. It enables a close check to be kept on his progress. The basic principle of treatment is to give vitamin D in a dose which is adequate to cure the osteodystrophy without, however, producing toxicity. The osteodystrophy is kept under observation radiologically by frequent X-rays of the wrists and knees. While the epiphyses remain unfused, observation of growth in stature is a most important parameter, while in this particular patient the rate of correction of his knock-knee after stapling provided a further valuable measure. In addition, the plasma alkaline phosphatase always falls to [illegible]al as the bones heal.

Signs of vitamin-D overdosage are shown at first by excessive output of calcium in the urine (this is not determined as a routine, and is not shown in Fig. 13 because it can be interpreted only when renal function is moderately good), later by an increase of plasma calcium to over 10·5 mg. per 100 ml. (assuming a normal plasma-protein level (see Case 7)) and by symptoms of anorexia, lassitude, thirst, and an increase of plasma urea. Increases in plasma phosphorus and bicarbonate also usually occur during vitamin-D intoxication, but these changes are less specific, and we do not measure these substances so much for practical as for theoretical purposes. Different patients have quite different thresholds for showing symptoms of intoxication. Some show symptoms at all plasma-calcium levels of over 11 mg. per 100 ml., others not till it rises to over 15 mg. The same patient, however, usually shows the same threshold over a long period of time.

It is of especial importance, in view of the slow action of vitamin D and of its cumulative effects, to use only a brief, if any, loading period when the vitamin is first given, and as soon as possible to treat with the expected necessary dose, which is of the order of 0·5 to 2 mg., but varies considerably from case to case. Most of our patients (not, however, patient No. 4) after the bones had been fully healed showed very low requirements for maintenance of healing, often as low as 0·25 mg. daily, or even 0·25 mg. on alternate days. It is important to try not to change the dose very frequently, or results will be impossible to interpret; other supporting treatment such as, in this case, sodium bicarbonate, should be changed even less frequently. When intoxication occurs, the vitamin D should be stopped altogether for a week or more, and then restarted at a lower dose.

Note from the chart a temporary intoxication while the patient was being loaded with AT10 on his first admission. This alarmed us so that we under-treated him for a while, and during the period December 1954 to July 1955 his rickets (as seen by X-rays) worsened, his growth-rate fell, his knock-knee failed to lessen, and the plasma phosphatase increased. He was thereafter adequately treated, but there was an episode of severe intoxication in July 1957, and a milder one in April 1958 which we were rather slow to deal with, since we were then surprised that he was now being intoxicated by a dose which was quite insufficient for him four years before. Note, too, that the recent reduction of DHT from 0·5 to 0·25 mg. per day (January 1959), on account of hypercalcaemia, has been followed by a steady rise in plasma phosphatase, so that we now (October 1959) have raised it to 0·5 and 0·25 mg. on alternate days. Perhaps we should add that our follow-up observation of this patient is made difficult by the fact that he lives nearly 200 miles away from us, and can attend only infrequently and for short periods at a time. Also we did not know much about this treatment until recently. Over the years there has been a very slow increase of plasma urea, which is of ominous portent. The greater temporary increases have coincided with hypercalcaemia. The patient has maintained a moderate haemoglobin level (about 90 per cent.). In a chronic case of this kind a fall in haemoglobin level usually heralds the terminal rise in urea.

Discussion

We have described here 14 consecutive uraemic patients admitted for special study on account of symptoms referable to the skeletal system. One, the least uraemic, was a child with dwarfism only; all the others had gross radiological signs of rickets (or osteomalacia) or hyperparathyroidism, or both. Certain general conclusions can be drawn from this study.

Our main objective was to secure relief from the bone symptoms and disappearance of radiological signs in the 13 most severely affected patients. This was uniformly successful in 10 of those who survived more than a month after beginning suitable treatment. The treatment was largely unsuccessful in one patient (Case 1) who survived for two years with treatment, but who was not adequately controlled according to the principles laid down later. The other two died quickly after admission. The mainstay of treatment has been adequate dosage with a form of vitamin D. At first we used AT10, but later changed it to pure dihydrotachysterol (DHT), so as to determine the action of a pure compound. In Cases 12 and 14 pure vitamin D_2 and D_3 respectively were given, with results very similar to those obtained with DHT. We have further unpublished data to suggest that there is no marked qualitative difference between these three pure compounds, although small differences in their rate of action and dosage equivalence may yet be discovered. We must stress here the point that DHT and AT10 are usually believed to have no antirachitic action. This is certainly not true in the rickets occurring with renal-glomerular disease, as is well shown in Plate 6, Figs. 32 and 33, which show a good beginning of healing with DHT as the only treatment. The value of alkalis (as sodium bicarbonate) in the treatment remains doubtful. When we have given sodium bicarbonate alone, as in our Cases 2, 9, and 14, the calcium balance (Figs. 1, 8, and 12) appeared to be just as abnormal and characteristic of the disease as in our other patients during their control periods without treatment. Many of our patients have shown an excellent response to treatment with vitamin D alone, a severe symptomless acidosis having persisted throughout. Hazards of alkali therapy were illustrated by one patient (Case 5) who rapidly developed tetany, and another (Case 3) who may have eventually died as the result of alkalosis. We have experience of other patients in whom pulmonary oedema and hypertensive crises may have been precipitated by alkalis. We must agree, nevertheless, that sometimes in renal disease patients feel a little better when given a small dose of alkali, and of course sodium in any form is of enormous value in those rare patients whose kidneys have a marked inability to conserve sodium ('salt-losing nephritis'). The usefulness of aluminium hydroxide also seems doubtful. The high plasma-phosphate level can certainly be lowered, but we have no evidence yet that this can be beneficial. After our experience with one patient (Case 3), in whom we believed we induced phosphorus-deficiency rickets with aluminium hydroxide (Plate 1, Figs. 14 to 16), we discontinued its routine use. We have therefore very few data about it. Our final conclusions are relatively simple, namely that the treatment of the

osteodystrophy requires a form of vitamin D given in adequate dosage for clinical, radiological, and biochemical response, but with very careful precautions (given in more detail earlier in this paper) against the great hazard of overdosage. There are no strong reasons for giving other drugs.

The metabolic findings are worth considering. We have fully confirmed the calcium balance data of Liu and Chu (1943), namely that in the untreated state the patient is in only slightly negative balance, with a level of faecal calcium about equal to the calcium in the diet, and a negligible amount in the urine. As these authors stated in their classic paper, the situation mimics closely that seen in ordinary vitamin-D deficiency. Neither their renal cases, however, nor ours responded to doses of vitamin D which cure deficiency rickets; indeed, Liu and Chu found that no change in calcium balance occurred with 10,000 i.u. (0·25 mg.) of vitamin D_2 daily. On the other hand, 3 ml. a day of AT10 (3·75 mg.) did alter the balance in the way expected for a definite vitamin-D action. They therefore stated that AT10 was effective when vitamin D_2 was not, a conclusion that has been extensively quoted in the subsequent literature. Our results, however, are at variance with this belief, since we have shown that all three forms of vitamin D act very similarly. It appears that Liu and Chu had not noted that the dosage they used of AT10 was 15 times as great as that of the vitamin D_2. This mistake has been repeated by others, for instance in the treatment of resistant rickets (van Creveld and Arons, 1954). This is a further reason why we prefer to quote all dosages on a weight basis, and why in the present study we have used the pure compounds when possible. It is of interest to note that Liu and Chu (1943), while succeeding in changing their patients' calcium balances towards normal with their large doses of AT10, did not proceed to treat them on a long-term basis and note whether the bones improved. Papers dealing with the therapy of the bone disease seem to be scarce, and we think that the present paper is the first to make consistent claims and provide details.

The variability of the bone dystrophy from case to case needs to be stressed. In Case 7 radiography showed a pure rickets, with no trace of hyperparathyroid changes. This is often believed to occur only as a consequence of cystinosis (Teall, 1954) or of primary renal-tubular malfunction; but this opinion must clearly be incorrect, since our patient was grossly uraemic from chronic nephritis. In Case 5, on the other hand, the patient had a remarkably similar history, but the radiological signs were those of almost pure hyperparathyroidism. Most of the other patients showed varying degrees of both rickets (or osteomalacia) and hyperparathyroidism. Review of the biochemical data also does not suggest an obvious reason for the differences between the bones in Case 5 and Case 7, nor why so many of the other patients had varying degrees of both changes, and some also had osteosclerosis. This confusing situation is similar to that occurring in the osteodystrophy of chronic steatorrhoea; there seems, therefore, to be no particular reason to attribute, as most other workers have done, the renal bone dystrophy to the known common consequences of renal-glomerular failure, such as low plasma calcium, high phosphorus, and acidosis. It is

perhaps more honest to admit that we do not know why the parathyroid gland enlarges and overacts in certain patients with renal failure. Neither do we know why all such patients show metabolic changes resembling those found in vitamin-D deficiency which, with the frequently accompanying bone changes of vitamin-D deficiency, can be corrected by giving very large doses of the drug. Liu and Chu (1943) speculated that an 'anti-vitamin D' compound might be circulating in the blood. We consider this to be a most reasonable hypothesis, especially since adrenal cortical hormones, such as cortisone, are now known to have an anti-vitamin D action in certain circumstances (Anderson, Dent, Harper, and Philpot, 1954). Perhaps it is also easier to hypothesize that it is the 'anti-vitamin D' compound which may also, in certain circumstances, stimulate the parathyroid glands, and that some similar compound is also responsible for the bone changes which so often occur in long-standing steatorrhoea. We should also clearly be aware of the theoretical possibility of an autonomous parathyroid tumour arising on one of the four hyperplastic glands as the result of prolonged stimulation in such a manner. We reported from this Department a patient with chronic steatorrhoea, in whom we believed that this process had occurred (Davies, Dent, and Willcox, 1956), and we are beginning to obtain data which strongly suggest that it may also occur in renal-glomerular failure. In such a case it may well be that vitamin D in large doses would not cure the hyperparathyroid changes in bone. One patient in the present series (Case 10) was unique in having gross ectopic calcification and a high calcium and phosphorus product in her plasma. She died before adequate studies could be made, but we already suspect from other evidence, not yet in publishable form, that this combination suggests a beginning autonomy of the parathyroid glands and, if so, that there may be a less satisfactory response to vitamin D. Clearly in such a case total parathyroidectomy, together with vitamin-D therapy, offers an alternative treatment that may sometimes be feasible.

A further point of theoretical interest concerns the reciprocal changes in plasma calcium and phosphorus levels shown by many of our patients while undergoing various treatments (Figs. 2, 5, 6, 7, 8, and 12). This reciprocation has been the subject of a special study by Philpot (1958) using data from this Department. In brief, artificial alterations of plasma-phosphorus levels in normal subjects are not followed by such immediate reciprocal alterations in calcium levels. Statements to the contrary have been made, among others, by Albright and Reifenstein (1948), who erected a complete theory of parathyroid hormone activity on this false assumption. The 'reciprocation' phenomenon, as we like to call it, does occur in certain bone diseases, among which are primary and secondary hyperparathyroidism. It has not been possible yet to explain it adequately.

The practical outcome of this work seems to be that, from the point of view of the treatment of the bone disease, there is no essential difference between our cases of severe renal-glomerular failure and those in which the bone disease has resulted from 'renal-tubular-insufficiency-without-renal-glomerular-insufficiency' (Albright and Reifenstein, 1948). The details of treatment may be

different, since alkalis are always stressed as the mainstay of treatment in the latter case, vitamin D, however, in large doses being recommended as well in order to hasten recovery. We are aware of no published cases in which alkalis alone have been given, but we have experience of three patients of our own whose bones have remained cured for many years with alkali alone, vitamin D having been given only at first. The question of the separate functions of alkalis and of vitamin D have been studied by Saville, Nassim, Stevenson, Mulligan, and Carey (1955), but only in two patients with the rather special form of renal tubular damage usually known as the Fanconi syndrome. They concluded that both substances were needed for adequate treatment of the bone disease.

We recommend, therefore, that one should look carefully for the bone complications resulting from prolonged renal damage. Sometimes these complications are a distressing additional cause of discomfort; rarely they have been for a while the patient's only complaint. In diagnosing renal-glomerular osteodystrophy one should recall not only the various radiological changes, illustrated here in gross degree, but more usually present in a much milder form, but also the fact that the alkaline-phosphatase level is raised early in the development of the bone disease, and is nearly always raised by the time symptoms have appeared.

We acknowledge gratefully the continuous help of our many collaborators in this study, the nursing staff and dieticians who performed the tedious balance studies, and the clinicians who by referring patients to us made this work possible. In order of relevant case numbers, the clinicians are: Mr. E. Devenish, Dr. J. C. Hawksley, Mr. G. K. Rose, Mr. H. Osmond-Clarke, Mr. D. Lloyd Griffiths and Dr. S. W. Stanbury, Mr. E. C. Bell-Jones, Dr. Mary J. Wilmers, Dr. T. St. M. Norris, Dr. C. Foster-Cooper, Mr. J. C. Anderson, Mr. H. H. Langston, Dr. J. Friend, Dr. J. E. Breese, Dr. G. Emmerson. The medical care of the patients at various times was assisted by Drs. J. Anderson, J. S. Penington, H. M. Lloyd, and G. Alan Rose. The photographs were taken by Dr. E. J. Huth, Mr. A. Bligh, and Mr. A. C. Lees. The charts were drawn by Mr. V. K. Asta. We thank especially Dr. C. J. Hodson for performing, and for his help in interpreting, the radiological investigations which form so large a part of this paper.

Summary

Thirteen patients (aged two to 52 years) with chronic renal failure and uraemia of varying aetiology, who had marked radiological signs of osteodystrophy, are described. The latter signs comprised degrees, varying in each case, of rickets (or osteomalacia), hyperparathyroidism, and osteosclerosis. In most cases the chief complaints of the patients at the time were referable to the skeletal system. A further patient with dwarfism only was also studied.

It was possible to treat 10 of these patients for a reasonable time with a form of vitamin D, and sometimes also with sodium bicarbonate. This treatment

was followed in all cases by marked symptomatic improvement and, if sufficiently prolonged, by a return to normal of the radiological signs of bone disease, and a lowering to normal of plasma alkaline phosphatase levels. This improvement occurred even though, in most cases, the renal damage was actively progressing and may have led in a few months to the patient's death. In some other cases the symptomatic and objective signs of improvement have been spectacular, and the patients, previously ill and crippled, have been able for some years to live fairly normal lives, in spite of continuing severe anaemia and plasma-urea levels of the order of 200 mg. per 100 ml.

The bone disease associated with severe renal-glomerular failure can therefore be treated as successfully as that caused by 'renal-tubular-insufficiency-without-glomerular-insufficiency'. The form of vitamin D given to most of our patients has been dihydrotachysterol (DHT) or AT10. The preliminary results with vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) suggest that they both have very similar actions in this disease, and that all three forms are similarly potent if compared on a weight basis.

Calcium balance data before and after treatment fully confirm the view that the untreated state very closely resembled that occurring in classical vitamin-D deficiency. The subsequent response to vitamin D also resembled the response of the deficiency disease to treatment, except that the required dose of vitamin D was much larger.

The place of alkalis in the treatment of this disease has not been fully assessed. It is already clear, however, that in many cases they are quite unnecessary, the patient making an excellent recovery in spite of the continuance of low plasma-bicarbonate levels and low blood pH.

The usual dangers of vitamin-D intoxication are present in these cases, but are even more serious than usual, since there is little reserve of renal function. A scheme of suggested dosage and of clinical control is put forward.

On considering the pathogenesis of this bone disease and the results of our treatment, we are dissatisfied with any of the current explanations that attribute it to such factors as acidosis or low plasma-calcium or high plasma-phosphorus levels. We could also discover no correlation between the clinical and biochemical data on the one hand and the type of bone disease, as seen radiologically, on the other. On treatment with vitamin D alone the radiological signs of rickets and of hyperparathyroidism (or of both when present) healed simultaneously. In one patient who was also given aluminium hydroxide the rickets worsened as the hyperparathyroidism healed. The rickets rapidly healed when aluminium hydroxide was withheld, with no other changes in treatment. We suggest that this temporary rickets was due to phosphorus deficiency induced by aluminium hydroxide, a situation not previously described in man.

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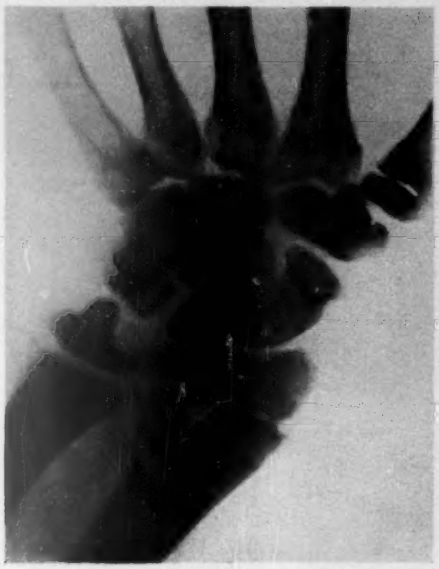

FIG. 14

FIG. 15

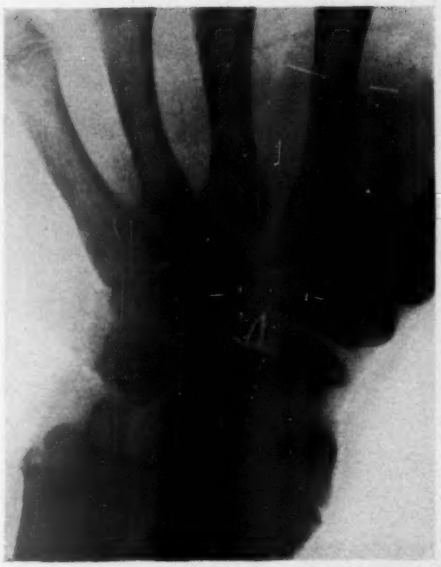

FIG. 16

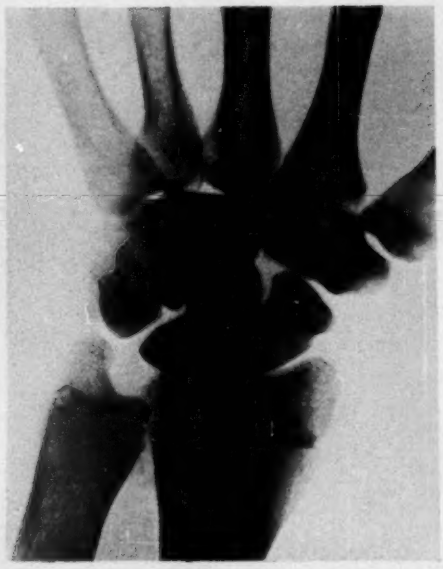

FIG. 17

FIGS. 14 to 17. Wrists of James L. (Case 3). His untreated state is shown in Fig. 14 (25.1.54). There were also marked hyperparathyroid erosions in the phalanges. Erosions can also be seen in the ulnar metaphysis. Fig. 15 (16.9.54) shows the worsening of his rickets while under treatment with dihydrotachysterol and aluminium hydroxide. All hyperparathyroid changes had, however, disappeared in this and subsequent films. Fig. 16 (8.12.54) shows the rapid healing of the rickets when aluminium hydroxide was stopped, dihydrotachysterol being continued in the same dose. Fig. 17 (1.4.58) shows the well healed wrist typical of his subsequent follow-up

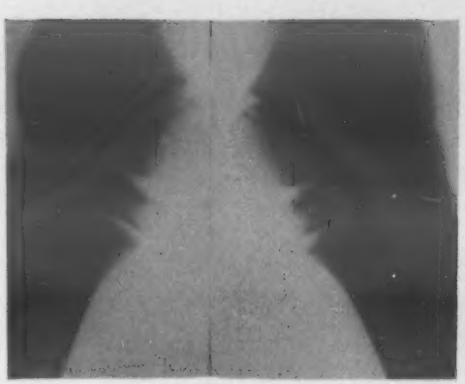

FIG. 18

FIG. 19

FIG. 20

FIGS. 18 to 20. Knees of Graham P. (Case 4). Fig. 18 (10.6.54) shows the marked rickets and knock-knee in the untreated state. Figs. 19 (11.10.54) and 20 (16.8.56) show the subsequent healing of the rickets and straightening of the legs. Good linear growth can also be seen from the position of the cyst in the left tibia with respect to the end of the bone

FIG. 21

FIG. 22

FIGS. 21 and 22. Graham P. (Case 4). Legs before (3.8.54) and after (8.4.57) the combined orthopaedic and medical treatment mentioned in the text

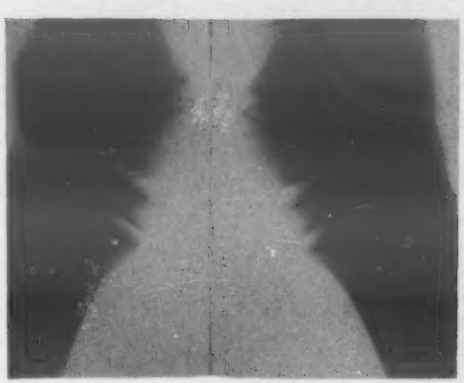

FIG. 18

FIG. 19

FIG. 20

FIGS. 18 to 20. Knees of Graham P. (Case 4). Fig. 18 (10.6.54) shows the marked rickets and knock-knee in the untreated state. Figs. 19 (11.10.54) and 20 (16.8.56) show the subsequent healing of the rickets and straightening of the legs. Good linear growth can also be seen from the position of the cyst in the left tibia with respect to the end of the bone

FIG. 21

FIG. 22

FIGS. 21 and 22. Graham P. (Case 4). Legs before (3.8.54) and after (8.4.57) the combined orthopaedic and medical treatment mentioned in the text

FIG. 23

FIG. 24

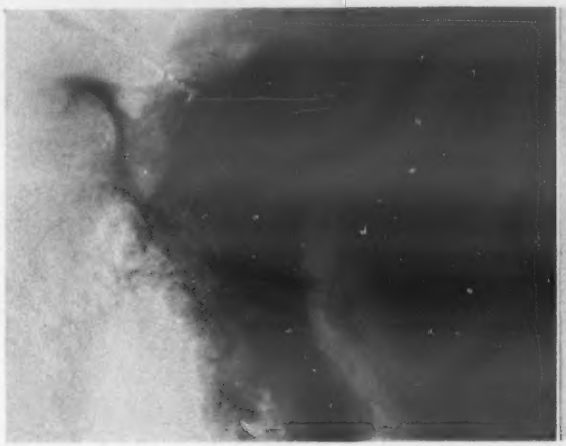

FIG. 25

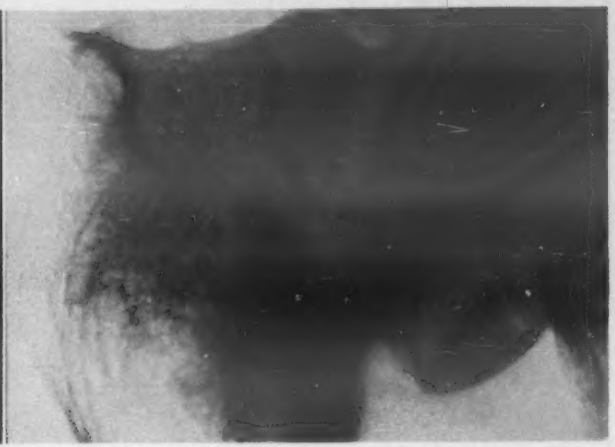

FIG. 26

FIGS. 23 to 26. Pelvis and hips of Sheila P. (Case 5). Figs. 23 and 25 (21.9.54) show gross hyperparathyroid changes in the femoral necks, with general fuzziness of the bones elsewhere. Figs. 24 and 26 (18.9.56), after treatment, show healing, with maintenance of the previous deformity. The trabeculae are no longer fuzzy, and are directed along the expected lines of stress

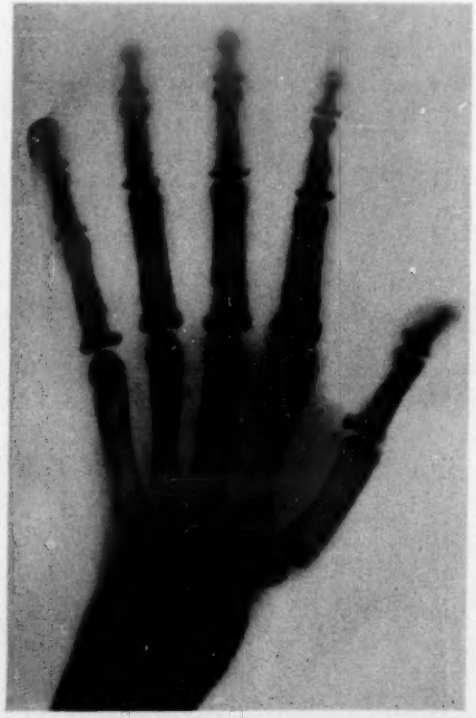

Fig. 27

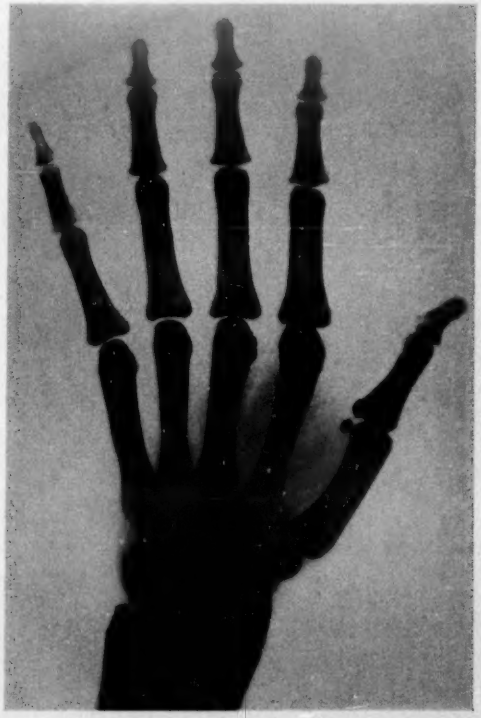

Fig. 28

Figs. 27 and 28. X-rays of the hand of Sheila P. (Case 5) before (21.9.54) and after (10.12.56) treatment. The gross hyperparathyroid erosions and early cyst formation before treatment have completely disappeared. The new bone formation from growth of ulna and radius is quite normal, but less dense than the healed bone seen just proximal to it. This indicates that there was a true osteosclerosis before treatment and that it has not changed subsequently

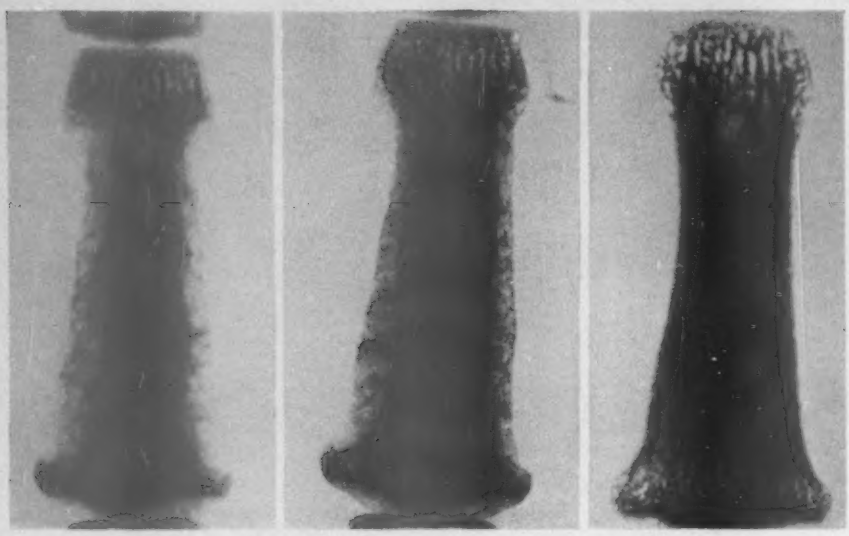

FIG. 29 FIG. 30 FIG. 31

FIGS. 29 to 31. Middle phalanx of the same finger of Sheila P. (Case 5). In Fig. 29 (21.9.54) gross parathyroid changes are seen before treatment. In Fig. 30 (1.11.54) early healing is already visible. The patient had by this time received loading doses of AT10 for only 20 days. Fig. 31 (10.12.56) shows normal bone formation after more prolonged treatment

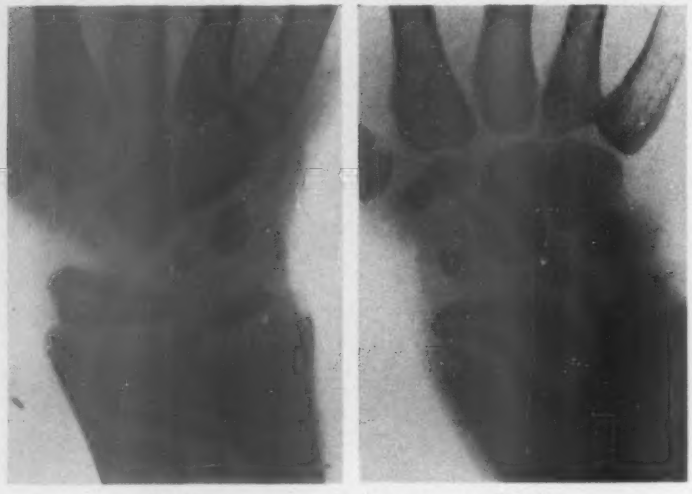

FIG. 32 FIG. 33

FIGS. 32 and 33. Wrist of Guy B. (Case 7) before (5.9.55) and soon after (2.1.56) beginning treatment. The rickets is rapidly healing on treatment with pure dihydrotachysterol. The patient died before a further picture with more complete healing was obtained. No hyperparathyroid changes were visible in the phalanx or elsewhere in this patient before treatment

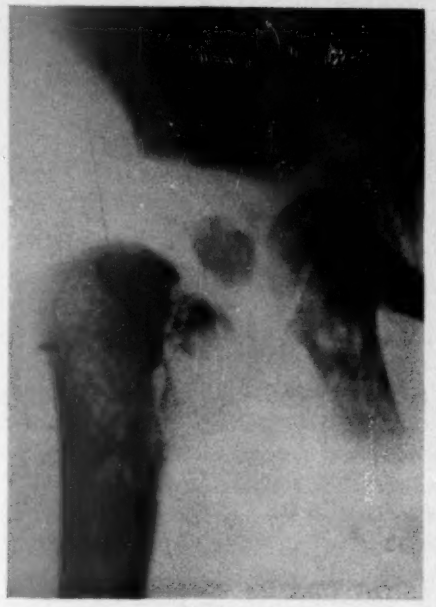

FIG. 34

FIG. 35

FIGS. 34 and 35. Right hip of Priscilla R. (Case 11) before (25.9.56) and after (30.11.56) the beginning of treatment with dihydrotachysterol. In this short time the fracture of the femoral neck has healed and good new bone formation is taking place

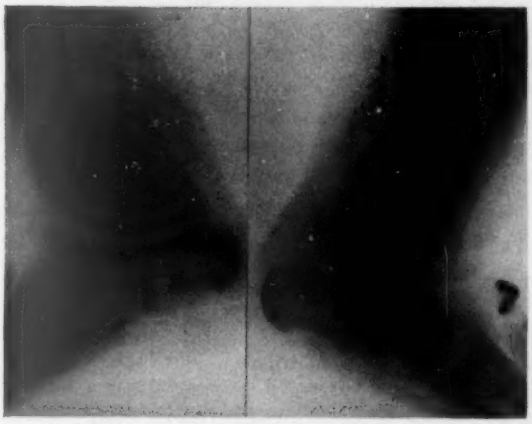

FIG. 36

FIG. 37

FIGS. 36 and 37. Ankles of Priscilla R. (Case 11) before (29.9.56) and after (7.1.57) treatment with dihydrotachysterol. In this short time considerable healing of the parathyroid erosion of the lower tibial metaphysis is visible. The fracture in the right tibia has healed, and both tibiae are beginning to straighten

616.5–003.24:612.67

SENILE PURPURA[1]

By S. SHUSTER and H. SCARBOROUGH

(From the Medical Unit, Cardiff Royal Infirmary)

With Plates 8 to 11

SENILE purpura, a condition well known to physicians, was first recorded by Bateman in 1817. He described the 'dark purple blotches of an irregular form and various magnitude' which he had noticed on the outer surface of the arms of elderly women. 'The health did not appear to suffer materially as in the other forms of purpura.' From a histological study of the skin removed from patients with senile purpura Tattersall and Seville (1950) were able to show 'degenerate collagen fibres in the affected areas', and they thought that the 'individual lesions are probably produced by minor external trauma acting on inadequately supported skin vessels'. Although this might explain the production of senile purpura, it seemed inadequate to account for the characteristic delay in the resorption of the extravascular blood, which may remain unchanged for weeks. Furthermore, another feature of senile purpura is that even relatively extensive lesions are not followed by the alterations in colour that normally succeed a bruise. It seemed difficult to account for this difference on purely structural grounds. When describing their histological preparations, Tattersall and Seville referred to the absence of cellular reaction around the extravasated blood. We were struck by this comment, and also by the apparent similarity of the lesions of senile purpura to those that are sometimes seen in patients treated with corticosteroids, for in such patients the inflammatory reaction is well known to be depressed and tissue collagen is altered (Siuko, Sävela, and Kulonen, 1959). It was thought that changes in structure and reactivity of ageing skin might serve as a starting-point from which the problem of senile purpura could be reinvestigated.

Methods

Thirty-five male and 51 female patients were studied. About one-third of these patients were in a geriatric unit. The remainder were out-patients, or were in an 'acute' general medical ward. With few exceptions, the patients were not suffering from serious disease, and none had any condition known to affect the skin. None had taken corticosteroids at the time of investigation, and none was known to have been suffering from a disease usually accompanied by

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purpura. No patient had rheumatoid arthritis, and none was suspected of having disseminated lupus or polyarteritis.

Lesions resembling those of senile purpura could be induced in suitable subjects by the injection of small amounts of their own blood into the skin. Silicone-coated tuberculin syringes were used for taking and injecting blood and other solutions. Needles were treated with 0·5 per cent. 'monocote' (Armour). Patients were given injections of 0·1 ml. of their own blood, directly or after it had been laked or diluted in saline. No anticoagulants were used. Blood was laked by adding one part of blood to two parts of sterile water and shaking; to serve as a control, one part of blood was added at the same time to two parts of physiological saline. Histamine weals were induced by pricking through histamine acid phosphate solution in a concentration of 1 mg. per ml. Two to four punctures were made through histamine both on the flexor and on the extensor surfaces of the forearms of patients with senile purpura. In some of the patients 0·1 ml. of old tuberculin (1 : 100, or 1 : 10) was injected into purpuric lesions. These relatively large doses were used because of the well-known difficulty of inducing a response to small doses of tuberculin in elderly persons (Caplin, Silver, and Wheeler, 1958).

Results

Experimental production of lesions resembling senile purpura. In patients with senile purpura it was found that intradermal injection of blood in certain areas of skin immediately produced lesions resembling senile purpura (Plate 9, Fig. 5). We recognize four main clinical characteristics of induced and spontaneous senile purpura:

1. Senile purpura occurs, and can be produced, only on the outer aspect of the forearms, the backs of the hands, and the sides of the neck and face.

2. The lesion is never raised above the skin surface; there is no bleb formation.

3. The haemorrhagic areas are irregularly shaped. They vary in size, tending to be larger the older the patient.

4. The colour of the lesion ranges from red to purple, but does not pursue the colour change seen after extravasation of blood into normal tissues or after injection into normal skin.

5. Senile purpura, spontaneous or induced, persists for one to three weeks or more. It thus lasts much longer than the lesions produced by injection of blood into parts of the skin not normally affected by senile purpura, and longer than those produced by injection into younger persons. The colour change is different from, and the length of time for which the lesions persist greater than, that which is observed after other forms of purpura.

Seventeen patients with senile purpura received injections, some on many occasions in various sites. In every case lesions resembling senile purpura were produced in areas of skin in which senile purpura had previously occurred. Intradermal injection of blood into other sites in these patients produced a typical intradermal bleb; this was true of the skin of the flexor surface of the arm, of the abdominal wall, and of the calf and shin.

It is possible to produce lesions typical of senile purpura in patients who have never had senile purpura, but only in areas of skin in which senile purpura occurs naturally. In patients who had never before had senile purpura the effect of injecting 0·1 ml. of the patient's own blood, freshly drawn, into the skin of various areas was examined in relation to the age of the patient. Three types of response were observed when blood was injected into the extensor surface of the forearm, namely a bleb, a lesion resembling senile purpura in all respects, and a lesion intermediate between a bleb and senile purpura. The same response was usually obtained over a relatively wide area of skin. Occasionally,

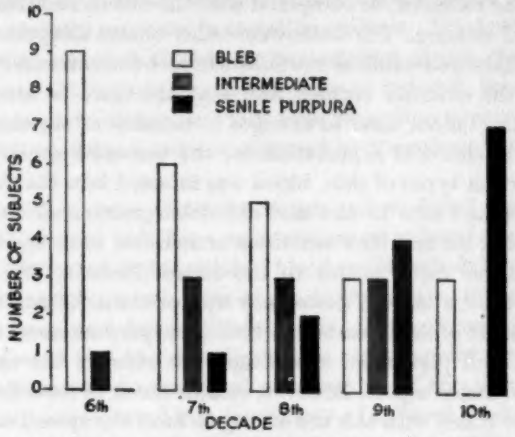

FIG. 1. The immediate response to injection of 0·1 ml. of blood into the extensor surface of the forearm in subjects without senile purpura.

however, the responses to injected blood differed in adjacent areas of skin, especially when injections were made at the periphery of a susceptible area, and in patients showing the intermediate type of lesion. As a standard procedure, therefore, the effect of one or two injections into the skin on the back of the forearm was compared with the response to blood injected into the flexor surface. In Fig. 1 the incidence of results obtained on the extensor surface is plotted against the age of the patients. After the eighth decade recollection of previous lesions may be incomplete, and some of the more elderly patients in whom lesions were induced may in fact have had senile purpura before. However that may be, intradermal injections of blood in patients without senile purpura are followed by typical lesions of senile purpura with increasing frequency as age advances. In the younger patients the intermediate type of response is more often found.

Most of the patients in the ninth and tenth decades had wasted arms, covered by the thin, atrophic, pigmented, and scarred skin with which senile purpura has long been associated clinically. Some, however, of the patients in whom senile purpura could be induced had plump arms. Injections were made in four young patients with various wasting diseases, in whom there was considerable

loss of subcutaneous fat. In all four subjects the response to injected blood was a bleb. The response of the skin to injected blood does not therefore appear to be related to general body wasting.

In attempting to induce senile purpura in elderly people by injecting their own blood into the skin, we were struck by our inability to produce an intradermal bleb in areas of skin in which senile purpura was to be expected but had apparently never occurred. Other liquids, including 0·9 per cent. saline, 1 per cent. procaine, tuberculin, Congo red, and laked blood, likewise failed to raise a bleb. In eight out of 12 patients with senile purpura the response to histamine punctures on the extensor, as compared with the flexor, surfaces of the forearm showed reduced wealing. The weals were either absent altogether or flatter and wider. This difference resembles the failure of bleb formation following injection of blood into the extensor surface, and may therefore be attributable to increased spreading rather than to changes in reaction of the skin to histamine. In seeking an anatomical explanation for the increased spreading of injected solutions in certain types of skin, blood was injected into the thin skin of scars in two patients, and into 15 new and old striae gravidarum in eight patients. It was found that normal bleb formation is modified in such skin, the injected blood spreading at right angles to the striae (Plate 8, Fig. 2). Similarly, spontaneous purpura in scar tissue may appear linear (Plate 8, Fig. 3). Skin on the flexor aspect of the forearm, in which senile purpura never occurs, becomes thin, atrophic, and pigmented in old age, like skin on the extensor surface. The skin of the flexor aspect, however, retains much of its collagen (Tattersall and Seville, 1950) and with this the ability to limit the spread of injected solutions, so that a bleb can be raised. These observations suggest that the abnormal spreading of injected blood may be determined by the changes in skin collagen which are associated with ageing. After an inflammatory reaction had been excited by the injection of tuberculin into an area of skin known to be susceptible to senile purpura, 0·1 ml. of blood was injected into a part of the inflamed area. In six out of seven patients the injection was followed either by bleb formation or by an intermediate type of response, the inflammatory exudate having apparently limited the lateral spread of the blood.

Although it is clear from these observations that excessive spread of extravasated blood results in the characteristic appearance of senile purpura, the initial cause of rupture of the vessels requires further explanation. Tattersall and Seville (1950) attributed the rupture of the vessels to 'trivial trauma acting on inadequately supported skin vessels'. Such a statement is too vague to be a really satisfactory explanation of the phenomenon. Furthermore, we have repeatedly observed that firm and prolonged digital pressure to the skin, exerted as close as possible to naturally occurring lesions, does not produce senile purpura. It can, however, be regularly produced simply by drawing a knuckle firmly across the skin, or by pulling laterally on a strip of adhesive tape applied to the skin (Plate 8, Fig. 4). The latter procedure excludes any effect of direct pressure, and presumably puts a shearing strain on vessels passing to the skin from the subcutaneous tissues.

Resorption of injected blood. The course of resorption of injected blood was related both to the type of lesion induced by the injection and to the age of the subject. When the induced lesion is a bleb, resorption begins within one to four days, with the development of the colour change characteristic of a bruise. The blood disappears first from the central part of the bleb, which becomes progressively paler in colour. These reddish-purple purpuric spots with pale centres have the appearance that some have described as characteristic of embolic purpura. This description applies equally well to blood injected into the skin of the legs, into the abdominal wall, and into the flexor aspect of the forearms, in both young and old subjects with or without senile purpura, except that resorption tends to be slower in the older patients. It is true also of resorption of blood from intradermal blebs on the extensor aspect of the forearms in younger subjects. Senile purpura, spontaneous or induced, takes one to three weeks, or even more, to disappear. This slow resorption is patchy, not regular as with a bleb. Resorption is not accompanied by the colour changes associated with bruising.

The injection of coloured solutions, Congo red, or laked blood, resulted in lesions resembling in size and shape spontaneous or induced senile purpura. It was a surprise therefore to find that laked blood, unlike whole blood, disappeared completely from the skin in a matter of one to three days, without showing the colour changes seen in a bruise (Plate 9, Fig. 5*a*, *b*). Even in young people laked blood injected into the skin disappears more rapidly than whole blood. These differences led to a histological examination of the skin after intact or laked blood had been injected into it. Biopsy of induced senile purpura in six patients, from six to 22 days after the injection into the extensor surface of the forearm, showed intact red blood-cells lying free in the atrophied skin (Plate 10, Fig. 6). A similar result was obtained by Tattersall and Seville (1950) in spontaneous senile purpura. On the other hand, after injection of blood into the flexor surface of the forearm, biopsy in six patients with spontaneous or induced senile purpura showed an inflammatory response in the skin three to four days later, with phagocytosis of the blood. The cells responding to injected blood were invariably mononuclear phagocytes, presumably tissue histiocytes (Plate 10, Fig. 7). Polymorphonuclear cells were rarely seen in these lesions, and were never phagocytic. Injected laked blood did not induce an inflammatory response in the five patients from whom skin was taken one to three days after injection. It appeared, therefore, that the absence of an inflammatory reaction to the extravasated blood in senile purpura might account for the characteristically slow resorption of the lesions, since once the cells are broken down, as in laked blood, resorption is rapid. The effect of inducing an inflammatory cellular response was therefore studied. Tuberculin, in a dose sufficient to produce an area of erythema and induration, was injected into spontaneous lesions of senile purpura in three patients, and into induced lesions in eight patients. Fresh blood was injected close by as a control. The patches of senile purpura disappeared in every case in two to four days, while the control lesions were relatively unchanged (Plate 11, Fig. 8). Sections of three lesions induced by tuberculin

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revealed the expected inflammatory cellular reaction, with an occasional intact erythrocyte.

Discussion

Senile purpura can readily be induced by the injection of blood into certain areas of skin in the elderly. The characteristic shape of induced senile purpura appears to be due to increased spread of injected blood, with failure of bleb formation. Increased spreading of injected liquids is seen only in skin in which senile degeneration of collagen is extreme, namely the extensor surface of the arms, wrists, and hands, and the sides of the neck and face (Tattersall and Seville, 1950; Tunbridge, Tattersall, Hall, Astbury, and Reed, 1952). It is therefore reasonable to suppose that the normal collagen network is largely responsible for the immediate limitation of spread of intradermally injected fluids, with consequent formation of a bleb. This view gains some support from the abnormal spreading of blood injected into wound scars or striae. Abnormal spreading does not occur if the injection is made into inflamed skin, even if the skin is known to be susceptible to senile purpura. This observation is in keeping with an anatomical explanation of abnormal spreading, the inflammatory exudate now filling the larger gaps between the atrophic collagen fibres.

The skin of elderly people in regions susceptible to senile purpura is freely movable over the deeper tissues. This is presumably the result of the atrophy of collagen, which now no longer binds them firmly together. This atrophy, together with the excessive lateral movement of the skin on the subcutaneous tissues which is permitted by it, may lead to rupture of the skin, and this may actually be felt to take place. Usually the fracture in the skin is seen as a haemorrhagic V-shaped tear, which later heals forming a small white scar. Such scars are often found on the extensor surfaces of the forearms of elderly people, and are usually an indication that senile purpura occurs, or can be produced, in that area. Our observations suggest that excessive lateral movement of the skin may shear small blood-vessels running between the freely mobile skin and the subcutaneous tissues. It is in this way that senile purpura is naturally produced by minor trauma.

The absence of an inflammatory cellular reaction to extravasated blood in senile purpura is presumably the explanation of the slow resorption of the individual lesions, since resorption is rapid when inflammation is induced with tuberculin. The characteristic discoloration of blood undergoing resorption, as in a bruise, appears likewise to be related to this cellular response to whole blood, since haemolysed blood, which is absorbed without an inflammatory reaction, does not show these colour changes during its resorption. These findings are in line with the work of Rich (1924) and of Muir and Niven (1935), who found that the breakdown of haemoglobin in the tissues to haemosiderin and 'haematoidin' (bile pigment) is an intracellular process, the cell involved being the phagocyte. The mechanism by which injected or extravasated homologous blood excites phagocytosis is of interest. Damage to the skin with the hypodermic needle, and increased tissue tension around an intradermal

bleb, could conceivably contribute to the inflammatory response. These factors, however, are unlikely to be very important, because there is no inflammatory response when haemolysed red cells are injected. The absence of inflammatory cells in the lesions of senile purpura could be due to a local abnormality in the skin, or to a general reduction of tissue response in the aged. The latter phenomenon has been observed, for example, with the tuberculin reaction (Caplin, Silver, and Wheeler, 1958).

It has been shown (Scarborough and Shuster, 1960) that the mechanism of corticosteroid-induced purpura is remarkably similar to that of senile purpura. The lesions in corticosteroid purpura are easily induced by a shearing strain to skin in which, as in senile purpura, there is gross degeneration of dermal collagen; while persistence of the extravasated blood is due to impaired phagocytic response to the blood. Collagen fibrils are said to be laid down by the fibroblasts, and it is therefore of interest that some histologists consider that the fibroblast may undergo transformation to a phagocyte (Maximow, 1957). If this is so, then not only the abnormal collagen but also the abnormal phagocytic response, in skin with senile purpura and corticosteroid purpura, might be related to reduced fibroblastic activity, which would then be the basic abnormality in both these conditions.

We are greatly indebted to Dr. G. F. J. Thomas for access to his patients in the Geriatric Unit of St. David's Hospital, Cardiff, and to Mr. Ralph Marshall of the Photographic Department of the Cardiff Royal Infirmary.

Summary

1. Lesions resembling senile purpura can be induced by the intradermal injection of blood on the extensor surfaces of the forearms, the backs of the hands, and the neck, in patients with senile purpura.

2. In areas of skin normally affected by senile purpura the injection of blood never produces a bleb, which is the response normally obtained in other parts of the body. The failure to raise a bleb and the increased spreading of injected blood within the tissues are related to senile degeneration of collagen in these sites.

3. These phenomena are related to ageing, since intradermal injection of blood into the extensor surface of the forearm in patients without senile purpura results in increased spreading with increasing age of the subjects.

4. Senile purpura is produced naturally by a shearing strain to the skin. This tears the vessels passing to the skin because of the excessive mobility of the latter on the subcutaneous tissues in elderly subjects.

5. Resorption of laked blood is normal and rapid from skin susceptible to senile purpura, but resorption of whole blood is slow both from spontaneous and experimentally induced senile purpura. This delay is due to the absence of the normal phagocytic response to extravasated blood, and resorption of the lesions is rapid if an inflammatory response is induced by tuberculin in a patch of senile purpura.

6. It is concluded that in elderly subjects excessive mobility of the atrophied skin permits rupture of the vessels by very slight shearing strains. Abnormal spread of the blood is permitted by the atrophied collagen fibrils, and the extravasated blood is resorbed slowly, and without the normal colour changes associated with a bruise, because of the absence of a normal phagocytic response to the blood.

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FIG. 2. The linear spread of blood injected into striae gravidarum is compared with the intradermal bleb formed when blood is injected into normal skin by the side of the striae

FIG. 3. Purpura in a scar from a patient with idiopathic thrombocytopenia. The linear spread of the extravasated blood is apparent

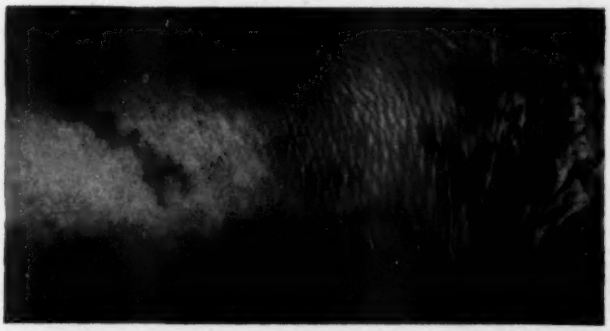
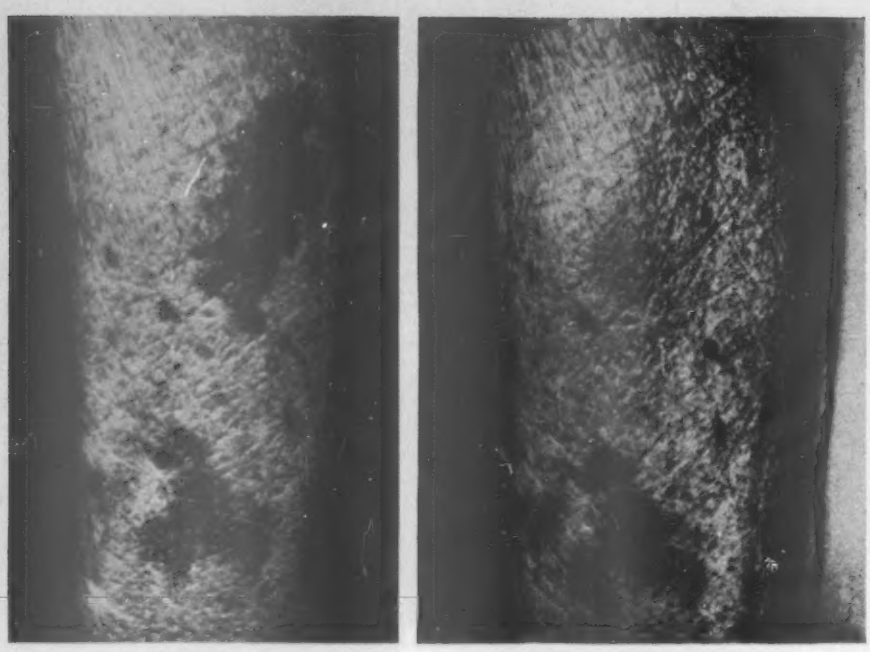


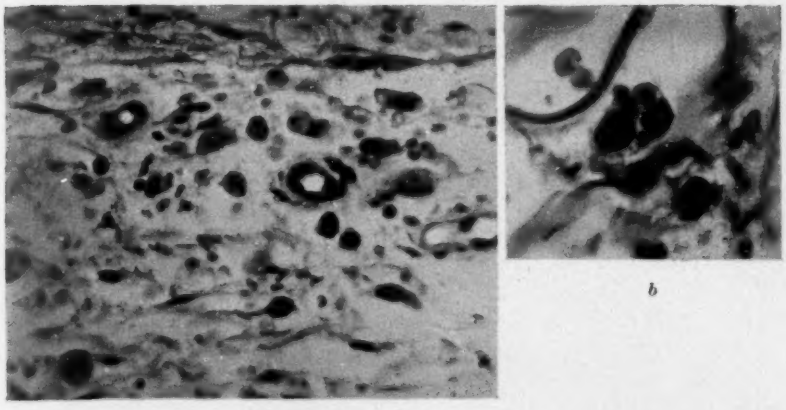
FIG. 4. To show purpura induced by a shearing strain to the skin. This patient had senile purpura on the dorsum of the hand. Neither pinching nor pressure resulted in fresh purpura, whereas stroking with the back of the knuckle immediately produced the lesions which can be seen on the extensor surface of the forearm



a *b*

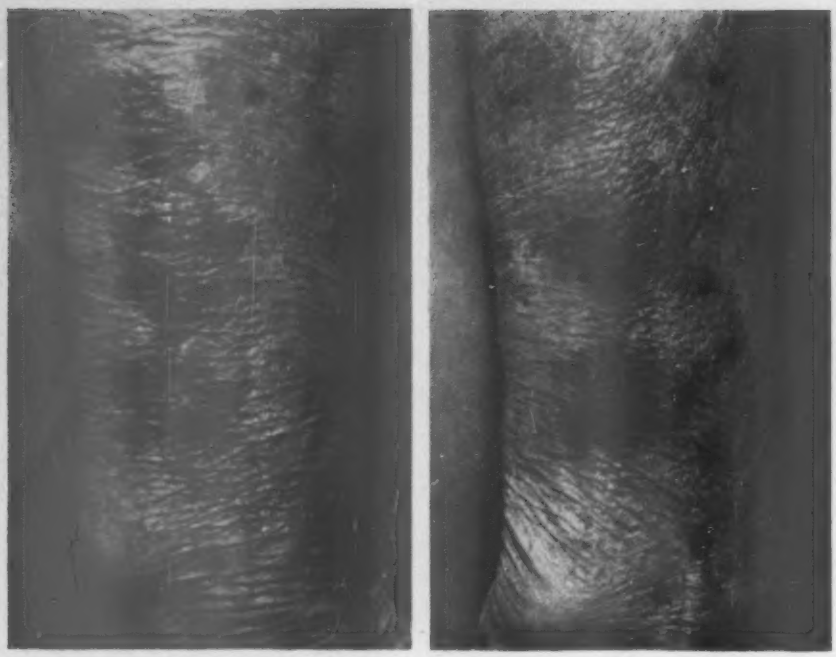
FIG. 5. Showing the rapid resorption of laked blood compared with whole blood. (*a*) Upper lesion: 0·1 ml. of one part blood laked with two parts water. Lower lesion: 0·1 ml. of one part blood mixed with two parts 0·9% NaCl. (*b*) One day later: laked blood resorbed, but intact erythrocytes unchanged

FIG. 6. Histological section (×450) of a lesion resembling senile purpura, 10 days after its induction by injection of blood. The atrophic epidermis and dermal collagen can be seen. There is no phagocytic response to the erythrocytes



a *b*

FIG. 7. (*a*) Section of skin ×360, from the flexor surface of the arm; the same patient as Fig. 6, three days after the injection of blood. Numerous phagocytes can be seen among the erythrocytes. (*b*) The same section ×880, showing a phagocyte containing erythrocytes



a *b*

FIG. 8. Resorption of blood after tuberculin reaction

(*a*) Three purpuric lesions were induced by injection of 0·1 ml. of blood. 100 units of old tuberculin were injected into the uppermost lesion

(*b*) Four days later. The uppermost purpuric patch has been resorbed. There is some resorption of the central lesion due to the spread into it of the tuberculin reaction. The lowest purpuric lesion remains unchanged

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COLLAGEN DISEASE AND THE CHRONIC BIOLOGICAL FALSE POSITIVE PHENOMENON[1]

By R. D. CATTERALL

(From the London Hospital)

RECENT progress in the serological diagnosis of syphilis, and the introduction of new, specific tests for treponemal diseases, have stressed the frequency and importance of non-syphilitic reactions of the type usually known as the biological false positive phenomenon. Moreover, it has been shown that the significance of non-specific reactions is frequently serious, and that they often have a grave prognostic importance. The present paper reports the experience at a large venereal disease clinic of a London teaching hospital over a five-year period, during which patients with possible non-syphilitic reactions were subjected to detailed study and prolonged follow-up.

Standard Serological Tests for Syphilis

Serological tests for syphilis were introduced 55 years ago by Wassermann, Neisser, and Bruck (1906). Using the Bordet–Gengou phenomenon of complement fixation, they commenced a new era of diagnosis of the treponemal diseases. Wassermann (1907) used foetal syphilitic liver as the antigen, on the assumption that the treponemes in the liver provided the antigenic substance, but it was later demonstrated that the test was non-specific in the immunological sense, and that extracts from various normal animal tissues provided satisfactory antigen. Flocculation tests for syphilis were first described by Michaelis in 1907. He also used syphilitic liver as the antigen. This method did not become popular until 1917, when it was reintroduced by Meinicke. He showed that treponemes or their products were unnecessary for the test, and used an extract of healthy beef heart as his antigen. Since that date many flocculation tests have been described. The ones most commonly used are named after their originators, such as Kahn, Price, Eagle, Hinton, Kline, and the Venereal Disease Reference Laboratory (V.D.R.L.). Serological tests based on complement fixation and flocculation have become highly standardized during recent years, and a considerable degree of sensitivity and specificity has been attained. The tests differ from each other only in minor technical details, and are dependent on the same basic physicochemical and immunological processes. The antigen most commonly used today in standard serological tests for syphilis is an alcoholic lipoidal extract of some normal animal tissue, usually beef heart.

[1] Received January 15, 1960.

It has been purified by many workers, and Pangborn (1941) has demonstrated that the antigenic component of the extracts is a pure chemical substance called cardiolipin, which is a phospholipid.

The antibody which is detected in the serum of syphilitic animals and in man by these non-specific antigens has been called 'reagin'. It is known to

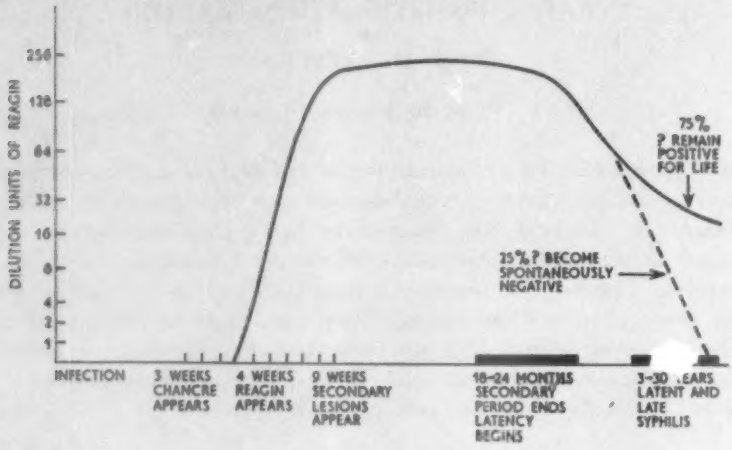

Fig. 1. Behaviour of reagin in untreated syphilitic infection in man. (After Moore and Mohr, 1952*a*.)

have a molecular weight similar to that of other antibodies, and to be associated with the gamma globulin fraction and, to a lesser extent, with the beta globulin fraction of the serum. Little is yet known about its immunochemistry. A great deal is known about the behaviour of reagin in the treponemal diseases, whether it be syphilis, yaws, pinta, or bejel. It has also been extensively studied both in experimental animals and in man, in both treated and untreated infections. Reagin begins to appear in the serum one week after the development of the primary chancre, and increases rapidly in titre for the next five to six weeks, usually reaching its maximum at about the time of the secondary manifestations. If the patient remains untreated it tends to become stabilized at about the same level for a period of about two years, and then, in the ensuing years, to decrease in amount. In some untreated cases it tends to disappear spontaneously, but in others it persists for the rest of life, but often at a lower level than in the earlier years (see Fig. 1). In treated patients, if treatment is started before the appearance of reagin in the serum, it may never appear, and the patient will then remain seronegative. In seropositive early syphilis reagin usually disappears within a few months of the start of treatment, usually about the sixth month. In late syphilis of all types the usual effect of treatment is to reduce the titre of reagin, but not to cause it to disappear, and the patient often remains seropositive (see Fig. 2). Unfortunately, while reagin appears in considerable quantity in the serum of animals and man infected with certain

treponemes, it, or a similar substance, is also present in minute quantities in the serum of all normal human beings (Kahn, 1951). In most cases the quantity is so small that it is not detected by standard serological tests, because they are usually adjusted for sensitivity and specificity so that this effect is excluded. In the treponematoses yaws, bejel, and pinta, each caused by an organism

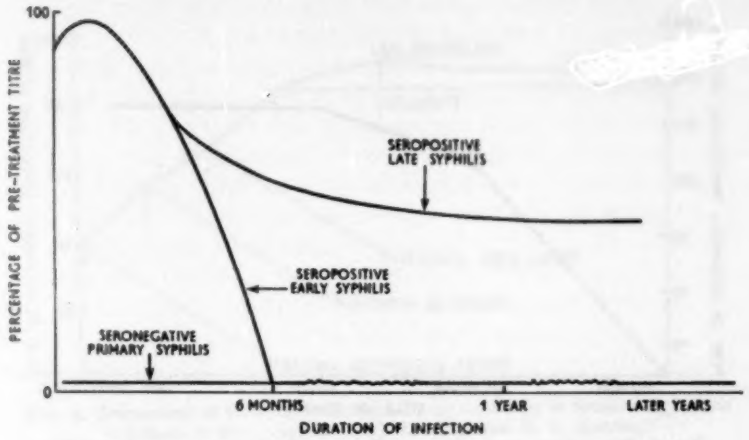

FIG. 2. Usual behaviour of reagin in treated syphilitic infection in man. (After Moore and Mohr, 1952*a*.)

indistinguishable from *T. pallidum*, positive serological tests are found with the same frequency as in syphilis.

The Treponemal Immobilization Test

In 1939 Turner, while studying natural immunity to syphilis, showed that the serum of syphilitic animals and man contained an antibody which combined directly with virulent *T. pallidum*. He incubated living organisms from rabbit syphilomata with normal and syphilitic sera, and then inoculated the mixture intradermally into rabbits' backs. When normal serum was used, typical chancres appeared at the site of inoculation. When syphilitic serum was employed, either there were no lesions, or the appearance of the lesion was modified or the incubation period prolonged. These experiments indicated the presence of an antibody in syphilitic sera that either destroyed *T. pallidum* or interfered with its virulence. Nelson (1948), working in Turner's laboratory at the Johns Hopkins School of Hygiene and Public Health, studied the unsolved problem of growing *T. pallidum* on artificial media. He succeeded in keeping the organisms alive, motile, and virulent, for five to 10 days on tissue-free artificial media. Nelson and Mayer (1949) mixed an emulsion of motile treponemes in this medium with normal and syphilitic sera in the presence of complement, and observed the results directly under the microscope. In the mixture containing normal serum, treponemes, and complement, nothing

happened within 15 to 18 hours, and the organisms remained motile and virulent. When syphilitic serum, either animal or human, was used, the treponemes were immobilized and killed. Absorption experiments demonstrated that the responsible antibody was distinct from reagin. There are then at least two antibodies or antibody fractions present in the serum in syphilitic

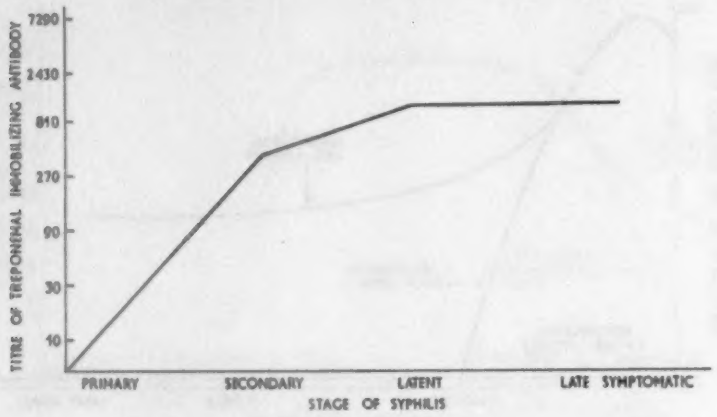

FIG. 3. Titre of treponemal immobilizing antibody in untreated syphilitic infection in man. (After R. A. Nelson.)

infections, and these are non-specific reagin and the treponemal immobilizing antibody. More recent work by d'Alessandro and Dardanoni (1953) in Italy and others elsewhere indicates that there may be more than two distinct antibodies or antibody fractions.

Further studies by Nelson, Zheutlin, Diesendruck, and Austin (1950) have shown that the treponemal immobilizing antibody does not occur in the serum of normal persons or of those suffering from non-treponemal diseases, but occurs uniformly in cases of syphilis and of the closely related treponematoses yaws, pinta, and bejel. It does not occur in other spirochaetal diseases such as leptospirosis, relapsing fever, rat-bite fever, or Vincent's infection. In untreated syphilitic infection its rate of appearance nearly parallels that of reagin. It is first detectable when the primary lesion is between five and 15 days old, rapidly increases in titre for the first few weeks, and reaches a peak about the second or third month of infection. Probably, though this has not yet been conclusively demonstrated, it does not spontaneously decrease in titre with the passage of years. Thus in the untreated syphilitic, from the secondary stage onwards, the specific antibody is almost always present for the duration of the patient's life, even though reagin may have disappeared spontaneously (see Fig. 3). The treponemal immobilization test is therefore a useful diagnostic procedure in patients whose serum is reagin-free, such as those with lesions possibly due to syphilis but with negative standard serological tests. It may, for example, help to differentiate between rheumatic and syphilitic aortic

incompetence, and in the diagnosis of certain neurological disorders. In treated primary, secondary, and early latent syphilis the antibody disappears from the blood as does reagin, but at a slower rate and not usually in a parallel manner. The sera of patients, therefore, who have been treated for early syphilis are found years later to be seronegative for both tests, though they are sometimes

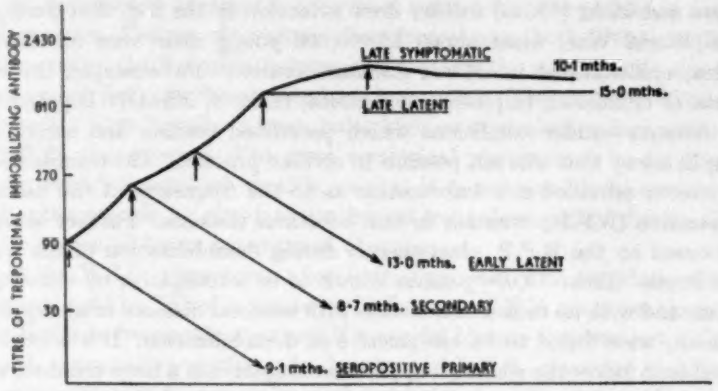

FIG. 4. Behaviour of treponemal immobilizing antibody in treated syphilitic infection in man. (After H. E. Zellman and R. A. Nelson.)

positive for immobilizing antibody and negative for reagin. With syphilis of several years' duration, treated late in the course of the disease, the immobilizing antibody does not disappear from the serum, though sometimes reagin may do so, and the sera of such patients, when examined from one to 35 years after clinically successful treatment for late syphilis of whatever type, are between 95 and 98 per cent. positive for the treponemal immobilizing antibody (Zellman, 1954) (see Fig. 4).

It thus appears certain that the treponemal immobilization test detects an antibody that is specific for syphilis and the related treponematoses. Unfortunately the test is expensive, and depends on maintaining a large rabbit colony infected with live treponemes. It is time-consuming, dangerous to technicians, complicated, and subject to many technical pitfalls, and its application is therefore limited to large medical centres.

The Biological False Positive Phenomenon

Most of the information concerning non-specific positive reactions or the biological false positive phenomenon has come from the United States of America. Moore and Mohr (1952*a*) have provided evidence that the phenomenon is far more frequent than was previously supposed. In 1938 a programme of mass blood-testing for syphilis was started in the United States. In 40 of the 48 States routine blood tests for all couples before marriage and for all pregnant women were required by law. Routine tests were and are still performed on

all personnel entering the armed Services, and again on demobilization. Many industries have made a practice of demanding a blood test before employment. In most hospitals tests are performed on all new patients, and many physicians have tests carried out as a routine in their practices. As a consequence millions of Americans have had these tests performed, and each year millions more are being tested.

Moore and Mohr (1952*a*) further drew attention to the fact that during the Second World War, when about 16,000,000 young men were mobilized in America, epidemics of infectious diseases occurred—for example, the exanthemata of childhood, respiratory infections, malaria, infective hepatitis, and other diseases—under conditions which permitted routine and serial blood testing in a way that was not possible in civilian practice. The combination of these events provided new information as to the frequency of the biological false positive (B.F.P.) reaction in the infectious diseases. Further attention was focused on the B.F.P. phenomenon during demobilization of the United States forces. About 75,000 persons known to be seronegative on entering the Services, and with no record of infection with venereal diseases or antisyphilitic treatment, were found to be seropositive on demobilization. It was obviously impossible to follow the whole group, but investigation of a large number, whose blood was re-examined to exclude technical error, led to the conclusion that less than half probably had syphilis, and more than half were probably B.F.P. reactors. Data accumulated by Moore and Mohr (1952*b*) in private practice amongst a white, well educated, and prosperous population group in the east of the United States indicated that about 40 per cent. of seropositive patients were not suffering from syphilis but had the B.F.P. reaction.

The B.F.P. reaction has been divided into two types, the 'acute' and the 'chronic'. The acute B.F.P. reaction is characterized by its occurrence during or shortly after a wide variety of unrelated non-syphilitic infections and illnesses. It disappears within a few days, weeks, or months—usually not more than six months—after recovery from the precipitating illness. Some common conditions producing the acute reaction are infectious mononucleosis, infective hepatitis, measles, chicken-pox, upper respiratory infections, virus pneumonia, malaria, and recent vaccination or inoculation. It has been estimated that about 20 per cent. of the population are potential B.F.P. reactors in appropriate circumstances. Chronic B.F.P. reactions are characterized by the absence of precipitating factors which produce the acute reaction, and by the persistence of reagin in the blood for many months or years or even for a lifetime. The only infectious disease known to produce a high proportion of chronic B.F.P. reactors is leprosy, but, as leprosy is rare in Britain and the United States of America, it does not account for many of the known cases, and the clinical recognition of leprosy is not usually difficult.

Before the introduction of the treponemal immobilization (T.P.I.) test it was possible only to guess, on the results of a careful history, physical examination, and epidemiological investigation of the family and sexual contacts, whether the patient was a B.F.P. reactor or not. Zellman (1954) has shown

that the T.P.I. test is highly specific for syphilis, and studies of the test indicate that in careful hands it is highly reproducible (Sequeira and Wilkinson, 1955). Discrepancies are usually explained by technical errors, or by very low titres of antibody. It is reasonable to conclude, therefore, if repeated serological tests for syphilis are positive over a period of several months or years, and if there is no historical or clinical evidence of syphilitic infection and two T.P.I. tests are negative on separate specimens of serum, that the patient is a chronic B.F.P. reactor. The use of a variety of serological tests, both of the complement fixation and of the flocculation type, will increase the number of cases found. Disagreement between the various tests is common. The majority of reactions will be a low titre (8 units or less), but a high serological titre does not exclude the B.F.P. phenomenon. The same serological picture may be produced by syphilis, especially treated syphilis, so that it is not possible to recognize the B.F.P. phenomenon by standard serological tests alone, although its existence may be suspected by an experienced observer.

Once the B.F.P. phenomenon has been diagnosed with certainty, the next question should be 'What is the cause?' In acute B.F.P. reactions the precipitating factor is frequently apparent if a careful history is taken and a detailed physical examination performed. In chronic B.F.P. reactions the cause is frequently difficult to ascertain, and extensive investigation and prolonged follow-up are required. Clinical data from a large group of chronic B.F.P. reactors studied by Moore and Mohr (1952*b*) have shown that all the patients were white in race, that 70 per cent. were female, and that the phenomenon occurred chiefly in the young. Twenty-seven per cent. of the male and 48 per cent. of the female subjects were under 25 years of age at the time of discovery. In 62 per cent. the reason for the discovery of the positive tests was stated to be routine blood testing in healthy persons. The remainder had serological tests performed for more specific medical reasons. Epidemiological studies in the majority of cases showed no evidence of syphilis in the family or sex contacts. Seventy-three per cent. of the female subjects under 25 years of age were demonstrable virgins. Antisyphilitic treatment, in contrast to its effect in syphilis, had no effect on the serological tests in chronic B.F.P. reactors. Adrenal cortical hormones were said to reverse the positive results of serological tests to negative, but the results again became positive when the hormones were withdrawn. No such effect had been observed in the cases of proven syphilis. The cerebrospinal fluid was usually normal, but an increased protein content was observed in about 12 per cent. of cases. The family history in these cases revealed an unusually high incidence of collagen vascular diseases, including systemic lupus erythematosus and rheumatoid arthritis, as well as diabetes mellitus and major allergic conditions.

Moore and Lutz (1955) reported their findings in 148 chronic B.F.P. reactors followed up over a period of six years. Ten patients had proved systemic lupus erythematosus, forty-five had 'possible' systemic lupus erythematosus, not yet verified, seven had rheumatoid arthritis, and five had an unusual serious illness which had not been diagnosed. Laboratory investigations showed a mild

to moderate microcytic hypochromic anaemia, especially in women; occasionally more severe anaemia occurred, and there was usually a persistently increased erythrocyte sedimentation rate. There was sometimes leucopenia, leucocytosis, or eosinophilia. Lupus erythematosus cells were usually present only in cases of clinically recognizable systemic lupus erythematosus. Disorders of the globulin fraction of the plasma proteins were a common finding, and Moore and Lutz called this abnormality 'dysgammaglobulinaemia'. It was present in about 90 per cent. of the series as measured by cephalin-flocculation, thymol-turbidity, and serum-globulin estimations. Electrophoretic patterns showed the abnormality to be in the gamma and to a lesser extent in the beta fraction of the globulin. Hypercholesterolaemia was present in 40 per cent. of the cases. Only 13 of the 148 patients investigated and followed up had no abnormality other than the B.F.P. itself. From all these facts Moore and Lutz drew the following conclusions. The chronic B.F.P. phenomenon is frequent in occurrence, and is not innocuous. It can be diagnosed by means of the T.P.I. test with only a small margin of error, probably in the region of two per cent. It is more frequent in young female patients than in male patients, and is often discovered for the first time on routine blood testing. It is frequently followed by the development of proven or possible collagen vascular disease, especially systemic lupus erythematosus. It is still more frequently associated with haematological disorders and disturbances of the serum globulin. Patients, therefore, who show the chronic B.F.P. reaction require careful observation and investigation over a period of years, and provide special opportunities for studying the natural history of collagen disease, and especially of systemic lupus erythematosus.

The Present Investigation

Patients and method of investigation. All the patients described in the present paper attended the Whitechapel Clinic of the London Hospital or were seen in consultation at the request of other physicians. Many first attended because of non-syphilitic venereal infections; some had been diagnosed as cases of latent syphilis many years earlier, and were attending for observation after treatment. A few were found to have positive serological tests for syphilis (S.T.S.) when they volunteered as blood donors, and some were referred from antenatal clinics where routine blood tests had given positive results. Others were referred from different departments of the hospital, and some by outside physicians because of the discovery of positive S.T.S.

For the purpose of this investigation the chronic biological false positive reactor is a patient whose serum has shown positive S.T.S. in repeated tests for a minimum of one year, but in whose case there is no past history of syphilitic infection, no clinical evidence of syphilis on careful medical examination, two negative treponemal immobilization tests on different specimens of serum, and normal tests of cerebrospinal fluid. Patients whose sera showed temporary non-syphilitic reactions, that is to say, acute biological false positive reactions, which persisted for a limited period, usually less than six months,

and who were without other evidence of syphilis, were excluded from the series. A number of patients whose sera showed persistent positive reactions, about 20 in all, were also excluded because they ceased to attend during the period of follow-up, or because the complete series of investigations had not been performed. All the patients included in the series were seen personally and questioned in detail as to the medical history of themselves and their families. They were all submitted to one or more thorough physical examinations. S.T.S. were performed repeatedly on their blood sera over a minimum period of one year, and at least two T.P.I. tests and an examination of the cerebrospinal fluid were carried out. Detailed haematological studies, estimates of erythrocyte sedimentation rate, estimation of the total plasma proteins and the plasma albumin and globulin, thymol-turbidity tests, estimation of the serum cholesterol, and examinations of the peripheral blood for lupus erythematosus cells (L.E. cells), were performed at suitable intervals. The electrophoretic pattern of the plasma proteins was not investigated owing to lack of facilities. Other pathological and radiological investigations were performed in cases for which they seemed indicated. The period of follow-up varied from one to five years. Some of the patients who had been diagnosed as having latent syphilis before the T.P.I. test was available, and had been given antisyphilitic treatment, had been attending for surveillance for periods of up to 20 years. Others were seen at long intervals, but all had been observed for at least a year.

Clinical details. Most of the patients described came from working-class families of the lower educational group, and most lived in the east end of London. There were 54 patients, of whom 36 were women and 18 men. Of the 36 women 34 were white and two coloured; of the 18 men 15 were of European origin, two were Indians, and one Chinese. The ages ranged from 17 to 71 years. The majority (80 per cent.) of the patients, both male and female, were young, in the third and fourth decades of life.

Of the 36 women six (17 per cent.) have developed systemic lupus erythematosus, and L.E. cells have been demonstrated in the peripheral blood. One of these six patients died recently, and post-mortem examination showed changes compatible with a diagnosis of systemic lupus erythematosus. One woman had discoid lupus erythematosus with severe hypochromic anaemia, raised erythrocyte sedimentation rate, and abnormal liver-function tests, but as yet no L.E. cells have been found in her peripheral blood. Two patients have changes in the joints characteristic of moderately severe rheumatoid arthritis, but no L.E. cells have been found in their peripheral blood. The Rose–Waaler differential sheep-cell agglutination test was positive in one case and negative in the other. Two other women have developed Raynaud's phenomenon for which no cause has as yet been found. One middle-aged patient has acquired haemolytic anaemia, which is well controlled by prednisone. Another patient has rheumatic aortic stenosis and incompetence, with electrocardiographic evidence of left bundle branch block. One patient has periodic attacks of unexplained fever and severe posterior uveitis, the cause of which is undetermined; one has a

serious undiagnosed illness which is possibly a collagen disease, and another has had a series of psychotic episodes. Thus, of the 36 female patients, 15 (42 per cent.) have serious disabling illness, including six with proven systemic lupus erythematosus, and one of these has died of a collagen disease. Another

TABLE I

Chronic B.F.P. Reactors

Sex	*Total*	*Systemic lupus erythematosus*	*Discoid lupus erythematosus*	*Other collagen disease*	*Possible collagen disease*	*Haematological abnormalities only*	*B.F.P. only*
Female	36	6 (16·7%)	1	0	9 (25%)	12	8
Male	18	0	2	1	3	4	8
Total	54	6	3	1	12	16	16

TABLE II

Laboratory Abnormalities

Sex	*Total*	*L. E. cells*	*Anaemia*	*Raised erythrocyte sedimentation rate*	*Abnormal liver-function tests*	*Increased serum cholesterol*
Female	36	6	16	18	8	2
Male	18	0	2	3	2	1
Total	54	6	18	21	10	3

TABLE III

Clinical Manifestations Occurring with the B.F.P. Phenomenon

Arthritis or arthralgia, frequently limited to the small joints of the hands
Cutaneous lesions, such as discoid lupus erythematosus
Fever, malaise, and fatigue, often episodic but frequently prolonged
Haematuria and nephritis
Haemolytic anaemia
Hypersensitivity, especially to penicillin
Neurological lesions
Ocular lesions, usually posterior uveitis
Pleurisy, pericarditis, and involvement of other serous cavities
Photosensitivity
Psychoses
Raynaud's phenomenon and cold sensitivity
Splenomegaly and sometimes associated hepatomegaly
Subcutaneous nodules

patient has discoid lupus erythematosus without evidence of systemic involvement. The remaining 20 (55·5 per cent.) feel well at the present time, but four of them have moderately severe anaemia, six persistently raised erythrocyte sedimentation rates, one abnormal liver-function tests, and one a persistently raised serum-cholesterol level. Thus, only eight (22 per cent.) of the 36 women have shown no clinical or laboratory evidence of disease up to the present time.

The findings in the group of 18 men were rather different. One patient died after a long and unusual illness, and was found at post-mortem examination to have polyarteritis nodosa and chronic nephritis. Two patients have discoid lupus erythematosus, and one of these also has severe peripheral vascular disease, leading to gangrene of the fingers and toes. Two patients have changes typical of rheumatoid arthritis, and one Indian patient has skin lesions on the nose suggestive of leprosy, but this diagnosis has not been proved. One patient has haemolytic anaemia, but the diagnosis of systemic lupus erythematosus has not been proved in his case. Another patient has had severe psychotic episodes. L.E. cells have not been demonstrated in the peripheral blood of any of the men. Haematological abnormalities are few, and the erythrocyte sedimentation rate was raised in only three cases. One patient has abnormal liver-function tests, with a raised serum-cholesterol level and clinical signs of enlargement of the liver, but no symptoms.

Of the whole series, a history of sensitivity to penicillin was obtained in 11 cases (20 per cent.). Eight of these patients were women, and three were men. Four patients had had very severe reactions when penicillin was administered to them. The reactions in the cases of the other seven were of the delayed type, such as skin rashes and swelling of the face and ankles. Intradermal tests were performed in four cases, and in each case the local reaction was so violent that this method of investigation was not repeated. Most of the patients had received only one course of penicillin, but about one-quarter had received two or more courses.

Illustrative Case Histories

The following very brief case histories illustrate some of the typical problems associated with the chronic B.F.P. reaction.

Case 1. The patient is a 39-year-old woman, who was first found to have positive S.T.S. at the age of 31 when she was pregnant. She was diagnosed as having latent syphilis, and given treatment with penicillin. One year later she began to have painful and stiff hands and fingers, with slight swelling of the wrists. This condition progressed for years despite various forms of treatment. At the age of 38 she complained of lassitude, shortness of breath, and worsening of her arthritis. The haemoglobin was 60 per cent., the erythrocyte sedimentation rate considerably raised, and L.E. cells were found in the peripheral blood on several occasions. She developed systemic lupus erythematosus seven years after the discovery of the B.F.P. phenomenon.

Case 2. A woman of 21 years. The S.T.S. were found to be positive when she volunteered as a blood donor at the age of 18. Two years ago she gave birth to a normal female child after a normal pregnancy and confinement. She has never had any clinical manifestations of illness apart from marked pallor. She has a mild hypochromic anaemia which is resistant to iron, and the erythrocyte sedimentation rate is persistently raised to about 60 mm. in one hour. No L.E. cells have been found in the peripheral blood. This is a fairly typical case in which the only abnormality so far detected is in the blood.

Case 3. A 49-year-old man. At the age of 28 he developed a patch of discoid lupus erythematosus on the face, for which he was treated at various times with bismuth, gold, local carbon-dioxide snow, radium, sulphonamides, and mepacrine. When aged 43 he was given penicillin for pneumonia, and had a severe reaction. Since the age of 47 he has suffered from bouts of tiredness and lassitude, and at the age of 48 was found to be anaemic, to have an enlarged spleen, and to have positive S.T.S. The haemoglobin was 70 per cent.; the direct and indirect Coombs tests were positive; the cold agglutinin titre was 1/128, and the Donath–Landsteiner test negative. The electrophoretic pattern of the plasma proteins was normal, and no L.E. cells were found in the peripheral blood or sternal marrow. During his stay in hospital his haemoglobin level fell to 57 per cent. On treatment with cortisone his haemoglobin responded satisfactorily, and his spleen became much smaller. He has haemolytic anaemia, possibly associated with systemic lupus erythematosus, although L.E. cells have not yet been demonstrated.

Case 4 is that of a 33-year-old married woman, who was first found to have positive S.T.S. after the birth of a still-born child five years previously. At that time her liver and spleen were noted to be palpable, and she had changes in the hands suggestive of rheumatoid arthritis. Two years later she again became pregnant, but miscarried, and became temporarily psychotic. She recovered, and six months later developed a pleural effusion. The haemoglobin was 43 per cent., and the erythrocyte sedimentation rate 58 mm. in one hour. There was also albuminuria. L.E. cells were found in the peripheral blood two years ago. Since then she has had a small maintenance dose of cortisone, and is moderately well. Systemic lupus erythematosus was diagnosed three years after the discovery of positive S.T.S.

Case 5. A 25-year-old male patient. He was discovered to have positive S.T.S. four years ago on routine blood testing, when he was suffering from non-specific urethritis. A right nephrectomy had been performed at the age of 18 years for renal tuberculosis. He had suffered from severe urticaria since childhood, and for the past five years had had mild arthritis of the hands, wrists, and ankles. One year ago he developed pain and swelling of the elbows, and increased pain and stiffness of the hands and wrists. The changes in the joints suggested rheumatoid arthritis. The erythrocyte sedimentation rate has been persistently raised, but no L.E. cells have been found in the peripheral blood.

Case 6 is that of a 27-year-old woman. When aged 19 she developed puffiness of the face, hands, and feet. When 21 and 22 years old she had severe attacks of uveitis. At this time her liver and spleen were found to be palpable. The following year she had a miscarriage at three months, and her S.T.S. were found to be positive. Shortly afterwards she complained of further blurring of vision, paraesthesiae in the legs, and weakness. At the age of 25 she developed Raynaud's phenomenon, and 'liver' palms were conspicuous. L.E. cells were found in the peripheral blood on several occasions. She is now a complete invalid with paralysis of the lower limbs.

The six cases described illustrate the fact that the manifestations of disease in patients with the chronic biological false positive phenomenon usually occur in episodes and tend to be chronic. They also demonstrate the diversity of the clinical manifestations, the difficulty of early diagnosis, and the variability of the course. Patients may remain symptomless for many years or even a life-

time, or may have a rapid, eventful, downhill course which progresses to severe invalidism or to death.

Discussion

It has not been possible to estimate the incidence of persistent non-syphilitic reactions in the sera of patients attending this venereal disease clinic in London, owing to the high defaulter rate. It appears, however, that the incidence is sufficiently high to warrant very careful investigation of all patients with positive serological tests for syphilis before a diagnosis of latent syphilis is made and antisyphilitic treatment given. At the present time the majority of cases of syphilis when discovered present the features of latent syphilis, and the problem of differential diagnosis is of great importance to those undertaking the care and treatment of such patients. At the present time the treponemal immobilization (T.P.I.) test provides the only certain method of differentiation between latent syphilis and the biological false positive (B.F.P.) phenomenon. Whether the recent advances in serology, which have provided such diagnostic aids as the Reiter's protein complement fixation test and the treponemal Wassermann reaction, will produce a new method which can displace the complicated T.P.I. test, is a matter for the future, and much work remains to be done in assessing new serological reactions.

The high incidence of penicillin sensitivity in the present group of patients makes it even more important that an accurate diagnosis between latent syphilis and the B.F.P. reaction is made before antisyphilitic treatment with penicillin is given to patients who are found to have positive serological tests. There is some evidence to suggest that penicillin may be harmful to chronic B.F.P. reactors, apart from the dangers of acute serious reactions during treatment. In the present series the onset of symptoms in at least two cases can be dated from the use of penicillin injections given in the belief that the correct diagnosis was latent syphilis. Further study of the mechanism of penicillin sensitivity and of the formation of antibodies following penicillin administration may help to clarify its importance in the chronic B.F.P. phenomenon.

The majority of patients in the present study were young women. Nevertheless, the incidence of the chronic B.F.P. reaction among male patients was higher than in other reported series. This is probably due to the fact that a much larger number of male patients were subjected to routine blood testing, the ratio of male to female new patients attending the clinic being of the order of five to one. The occurrence of systemic lupus erythematosus and other severe illnesses was, however, considerably higher among the female patients, and so was the appearance of haematological abnormalities. It appears, therefore, that the chronic B.F.P. phenomenon indicates disease with a more serious prognosis in women, although it is not without significance in men.

The evidence confirms the observation of Moore and Mohr (1952*b*) that the chronic B.F.P. reaction is one of the manifestations of collagen disease, and that the phenomenon may occur months, and even years, before the appearance of clinical manifestations. The underlying abnormality is probably an alteration

in the serum globulin, affecting principally the gamma fraction. It is also probable that this deviation of the globulin from normal accounts for the increased sedimentation rate, the abnormal results of turbidity and flocculation tests, the B.F.P. phenomenon itself, and the development of the L.E. cell phenomenon. Laboratory investigations have shown that a consistent sequence of abnormalities tends to develop in these cases. The B.F.P. phenomenon usually appears first, and is followed by an increase in the erythrocyte sedimentation rate and the thymol-turbidity test. Later there is an increase in the serum globulin, and much later, in some cases, L.E. cells are found in the peripheral blood. Manifestations of disease, when symptoms do develop, tend to occur in episodes and to be unpredictable. The symptoms may be mild, as in cases presenting arthritis of the hands or Raynaud's phenomenon, or they may be severe and run a rapid course to complete invalidism or even death. A proportion of the patients appear to continue in good health for long periods with no abnormality detectable apart from the B.F.P. reaction itself. From the evidence presented here it would appear reasonable to conclude that the finding of positive serological tests for syphilis in a patient with no other signs of syphilis no longer justifies a presumptive diagnosis of syphilis and the giving of antisyphilitic treatment 'just to be on the safe side'. Patients with positive serological tests for syphilis require detailed investigation including a thorough physical examination, not only for signs of syphilis but also for signs of other systemic diseases. The serological tests should be repeated at suitable intervals, and quantitative tests performed with either the complement fixation or the flocculation test. If the positive serological tests persist without signs of syphilis, the T.P.I. test should be performed. Ideally two such tests should be performed on separate specimens of serum. An examination of the cerebrospinal fluid should also be performed. In experienced hands the T.P.I. test is sufficiently reliable for a final diagnosis of the presence or absence of syphilis to be based on its results. Once the diagnosis of a chronic B.F.P. reaction has been established, periodic observation of the patient for evidence of systemic disease and repeated laboratory tests should be carried out, so that possible prophylactic measures and early treatment of the underlying disease can be considered.

I should like to thank Mr. Ambrose King for permission to record this series of patients, and the physicians and surgeons of the London Hospital for referring some of them. The treponemal immobilization tests were performed by Dr. A. E. Wilkinson, and I should like to express my thanks to him for his advice and help. I am indebted to Professor Clifford Wilson for his valuable suggestions.

Summary

1. A series of 54 patients, 36 women and 18 men, attending a large venereal disease clinic in London, were discovered to have persistent non-syphilitic reactions to standard serological tests for syphilis. During observation six women developed systemic lupus erythematosus, and one man developed polyarteritis nodosa.

2. Two patients in the series have died recently, one woman from systemic lupus erythematosus and one man from polyarteritis nodosa. Post-mortem examination confirmed the diagnosis in both cases.

3. The clinical and laboratory findings in cases of the chronic biological false positive reaction are discussed, and short histories of six typical cases are described.

4. A high incidence of sensitivity to penicillin is reported among these patients. The importance of the diagnosis between latent syphilis and the chronic biological false positive reaction is stressed.

5. The diseases of which the chronic biological false positive phenomenon is a manifestation appear to have a more serious prognosis in women than in men. The presence of such a reaction is an indication for detailed clinical investigation and prolonged follow-up in both sexes.

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THE EFFECT OF SEX AND PARITY ON THE INCIDENCE OF DIABETES MELLITUS[1]

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It has long been recognized that more elderly women than men develop diabetes mellitus. There is less agreement about the sex incidence in earlier life, but it is generally held that up to the age of 40 men and women are equally affected (Spiegelman and Marks, 1946; Harris, 1949; Pyke, 1956*a*). The reported results, however, are unreliable either because of the relatively small number of patients under 40 or because of lack of control figures from the general population. The excess of elderly women has been attributed to an association with obesity (Joslin, Dublin, and Marks, 1936). More recently interest has been aroused by the work of Pyke (1956*a*), who found that the excess of women was confined to those who had borne children, and became more pronounced with increasing parity. This idea is supported by the earlier work of Munro, Eaton, and Glen (1949), but denied by Steinberg (1958) and Vinke, Nagelsmit, van Buchem, and Smid (1959). We have examined the effect of sex and parity on the incidence of diabetes in a large number of patients taken from a population of known age, sex, and parity. We conclude that the incidence of the disease is closely related to previous childbearing, and that diabetes before the age of 45 is actually commoner in men than in women, and commoner in men than in women of all ages who have had less than two children.

Material

The data were gathered from those patients with proved diabetes who first attended the Diabetic Clinics at the General Hospital and the Children's Hospital, Birmingham, between 1949 and 1958. Table I shows that there were 5,441 patients in all, with an average of 218 men and 326 women each year. There is no evidence of selection by age or sex; about 80 per cent. of the patients lived in the City of Birmingham, and the remainder near it. It is therefore assumed that the clinics are representative of the diabetic population of Birmingham, and that comparison with census figures for Birmingham within the period 1949–58 is valid. In every case, apart from small children, the inquiry was made by one of the authors directly from the patient.

[1] Received February 9, 1960.

Results

Age and sex specific incidence rates. Table II and Fig. 1 give the number of newly diagnosed cases for each sex in five-year age-groups. In order to relate these figures to the age and sex structure of the general population, the numbers

TABLE I

Number of New Attendances each Year, 1949–58

Year	*Men*	*Women*	*Total*
1949	131	286	417
1950	159	335	494
1951	163	325	488
1952	213	314	527
1953	240	282	522
1954	247	367	614
1955	246	339	585
1956	260	330	590
1957	249	340	589
1958	273	342	615
Total	2,181	3,260	5,441

TABLE II

Number of Cases and Relative Incidence $\left(\frac{\textit{Diabetics}}{\textit{Population}} \times 10^3\right)$ *for each 5-year Age-group, Men and Women, 1949–58*

Age at diagnosis (years)	*Number of cases*		*Incidence* $\times 10^3$		*Ratio of men/women*
	Men	*Women*	*Men*	*Women*	
0–4	17	14	0·33	0·29	1·14
5–9	45	25	0·98	0·56	1·75
10–14	41	50	1·09	1·37	0·80
15–19	71	43	2·53	1·20	2·11
20–24	65	37	1·74	0·91	1·91
25–29	86	63	1·92	1·39	1·38
30–34	93	63	2·17	1·46	1·49
35–39	111	72	2·44	1·64	1·49
40–44	141	137	3·28	3·22	1·02
45–49	213	225	5·49	5·72	0·96
50–54	258	407	8·02	11·03	0·73
55–59	272	495	10·66	15·65	0·68
60–64	284	549	13·47	20·04	0·67
65–69	208	497	12·53	21·34	0·59
70–74	146	340	11·81	17·88	0·66
75–79	90	185	11·90	15·59	0·76
80–84	25	38	7·77	6·52	1·19
85–89	7	10	7·92	4·79	1·65
Total	2,173	3,250			
Not known	8	10			
Grand total	2,181	3,260			

in each group have been divided by the numbers of men and women in Birmingham in the same five-year age-groups. Figures for the age and sex structure of Birmingham are taken from the 1951 census, and the result multiplied by 10^3

to remove inconvenient decimals. The results, which express the relative incidence of newly diagnosed diabetes in Birmingham for both sexes, are shown in Table II and Fig. 2. Table II also shows the ratio of men to women at different

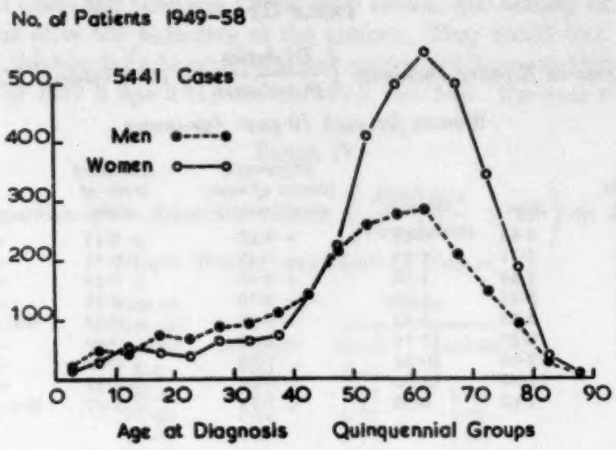

FIG. 1. Numbers of newly diagnosed cases in each five-year age-group.

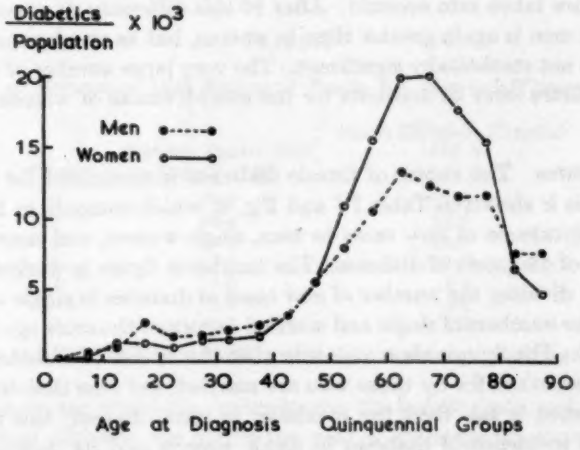

FIG. 2. Relative incidence of newly diagnosed cases in each five-year age-group.

ages, and Table III shows the statistical significance of these differences for different 10-year age-groups. The results show that diabetes starting before the age of 10 is commoner in boys than in girls. At puberty the sexes are almost equally affected, but between 15 and 19 there is again a predominance of boys.

The incidence remains about one and a half times as great in men for each five-year period up to the age of 40, and this difference is statistically highly significant. At 40, however, as the incidence in both sexes starts to increase, the

TABLE III

Difference in Relative Incidence $\left(\frac{Diabetics}{Population} \times 10^3\right)$ *between Men and Women for each 10-year Age-group*

Age at diagnosis (years)	*Men*	*Women*	*Difference (excess of men over women)*	*Standard error of mean*	*P*
0–9	0·64	0·42	+ 0·22	± 0·11	< 0·05
10–19	1·71	1·29	+ 0·42	± 0·21	< 0·05
20–29	1·84	1·16	+ 0·68	± 0·19	< 0·01
30–39	2·31	1·55	+ 0·76	± 0·21	< 0·01
40–49	4·33	4·43	— 0·10	± 0·33	Not significant
50–59	9·19	13·16	— 3·97	± 0·60	< 0·001
60–69	13·05	20·64	— 7·59	± 0·90	< 0·001
70–79	11·84	17·00	— 5·16	± 1·11	< 0·001
80–89	7·80	6·06	+ 1·74	± 1·57	Not significant

proportion of women rises and the difference between the sexes disappears. After 50 the incidence of diabetes is about one and a half times greater in women, even when the larger numbers of older women at risk in the general population are taken into account. After 80 this difference disappears, and the incidence in men is again greater than in women, but as numbers are small the difference is not statistically significant. The very large number of women who develop diabetes after 50 accounts for the overall excess of women having the disease.

Marital status. The excess of female diabetics is accounted for by married women. This is shown in Table IV and Fig. 3, which compare in 10-year age-groups the incidence of new cases in men, single women, and married women at the time of diagnosis of diabetes. The incidence figure is worked out, as in Table II, by dividing the number of new cases of diabetes in single and married women by the numbers of single and married women of the same age in Birmingham in 1951. The figures show not only that the excess of diabetes in women over 50 is accounted for by those who are married, but also that the incidence in single women is less than the incidence in men. Indeed, this relationship between the incidence of diabetes in single women and its incidence in men persists throughout life.

Parity is defined as the number of children born alive. In considering its effect on the incidence of diabetes in married women we have taken into account only those who were over 45 when diabetes was diagnosed, and had therefore completed their childbearing years. There were 2,551 women in this category, and in 2,318, or 90 per cent., we have a record of the number of children born

alive. In comparing their parity with the parity of the general population, the only national figures which include age are for married women aged 45–49 in the Fertility Report (1959) on the 1951 census. We are hampered by a lack of national figures for the parity of women aged more than 50. We cannot ignore age, for, as Glass and Grebenik (1954) have shown, the fertility of marriages has declined since the beginning of the century. They found that the mean number of children born to marriages first contracted between 1890 and 1899 was 4·28; by 1910 it was 3·11, and in 1920 it was 2·48. The year of marriage

TABLE IV

Comparison of the Relative Incidence $\left(\frac{Diabetics}{Population} \times 10^3\right)$ *in Men, Single Women, and Married Women*

Age at diagnosis (years)	*All men*	*Women*	
		single	*married*
0–9	0·64	0·42	..
10–19	1·71	1·27	1·91
20–29	1·84	0·87	1·33
30–39	2·31	1·44	1·57
40–49	4·33	3·48	4·59
50–59	9·19	7·88	13·99
60–69	13·05	9·12	22·36
70–79	11·84	7·82	18·36
80–89	7·80	1·93	6·69

TABLE V

Comparison of Percentage Distribution of Parity for Married Women aged 45–49

Parity	*Fertility Report 1959 (Census 1951)*	*Queen Elizabeth Hospital 1953–5 (1,571)*
0	20·2	21·8
1	26·4	27·3
2	23·9	25·7
3	13·1	12·9
4	7·0	5·5
*5–6	5·9	4·8
7+	3·5	2·0

* In the Fertility Report (1959) parities 5 and 6 are grouped together.

of the women we are considering extends over the last 60 years, and, irrespective of any effect of diabetes, the earlier the year of marriage the more fertile it is likely to have been.

We have used control data from the parity of 7,608 married women aged over 45 who were admitted to the Queen Elizabeth Hospital, Birmingham (a large general hospital) during 1953–5. The number of live births and the age on admission to hospital are recorded as a routine, and transferred to punch cards along with other basic information. We have felt justified in using these data because, as Table V shows, there is close agreement between the percentage

distributions of parity in women aged 45 to 49 in the national census of 1951 and in the control group of the same age from the Queen Elizabeth Hospital admissions. Table VI and Fig. 4 compare the percentage distribution of parity

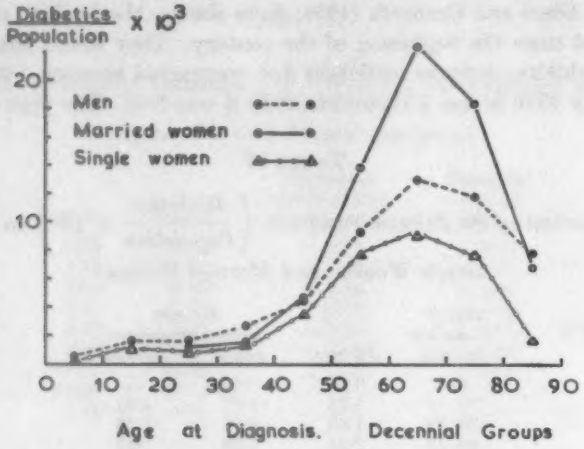

FIG. 3. The relative incidence in men, single women, and married women, in 10-year age-groups.

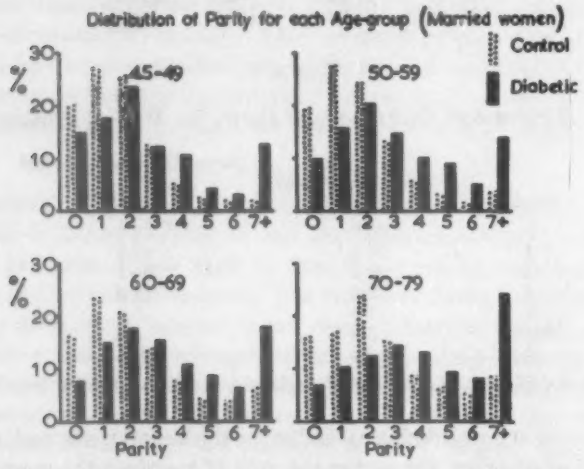

FIG. 4. Percentage distribution of parity in married women of each age-group; comparison of diabetics with control subjects admitted to Queen Elizabeth Hospital.

of the controls with that of the diabetics for different age-groups over 45. The results show that at all ages there is a deficit of married diabetic women having fewer than three children, and an excess of those having four or more. This excess is most apparent in those having seven or more children. The results

also show the general effect of age on the distribution of parity: with or without diabetes, the older a woman is the more likely she is to have had a large family. The same data are used in Table VII and Fig. 5 to show the relative incidence

TABLE VI

Percentage Distribution of Parity for each Age-group over 45, Diabetics and Controls (Married Women)

	Age 45–49		*Age 50–59*	
Parity	*Control Q.E. (1953–5)*	*Diabetics 1949–58*	*Control Q.E. (1953–5)*	*Diabetics 1949–58*
0	21·8	15·1	19·8	10·1
1	27·3	17·7	27·7	15·8
2	25·7	23·6	24·4	20·5
3	12·9	12·4	13·3	14·9
4	5·5	10·8	6·3	10·3
5	2·7	4·3	3·3	9·2
6	2·1	3·2	1·6	5·1
7+	2·0	12·9	3·6	14·1
Total number of cases	(1,571)	(186)	(2,754)	(760)
Mean number of children		2·9		3·5
	Age 60–69		*Age 70–79*	
0	16·3	7·8	16·2	7·0
1	23·6	15·0	17·7	10·4
2	21·9	17·7	23·5	12·4
3	14·3	15·5	15·4	14·5
4	8·3	10·8	8·7	13·4
5	4·8	8·7	6·5	9·5
6	4·0	6·5	3·2	8·4
7+	6·8	18·0	8·8	24·4
Total number of cases	(2,092)	(893)	(1,028)	(442)
Mean number of children		3·9		4·6

In the 39 cases diagnosed after the age of 80 the trend seen in the other age-groups was continued.

Q.E. = Queen Elizabeth Hospital.

TABLE VII

Incidence $\left(\frac{\textit{Diabetics}}{\textit{Population}} \times 10^3\right)$ *in Men, Single Women, and Married Women by Parity, for each Age-group*

Age at diagnosis (years)	*Men*	*Single women*	*Married women: parity*					
			0	1	2	3	4–5	6+
45–49	5·49	4·36	3·81	3·60	5·10	5·29	10·14	21·57
50–59	9·19	7·88	6·55	7·31	10·79	14·35	26·15	47·13
60–69	13·05	9·12	9·77	12·87	16·40	21·82	30·12	45·78
70–79	11·84	7·82	7·09	9·66	8·68	15·47	24·73	45·03
80–89	7·80	1·93	1·97	5·58	4·44	5·26	4·74	9·33

of diabetes in each parity group. These figures were obtained by dividing the number of diabetics by the number of women in the general population of the same age and parity. To arrive at the numbers of women in each age and parity group of the general population, we have assumed that married women admitted

to the Queen Elizabeth Hospital are representative of equivalent groups of the general population of Birmingham (Table V). Table VII also shows the relative incidence of new cases in men and single women. It is clear that at all ages there is a progressive increase in the incidence of diabetes with increasing

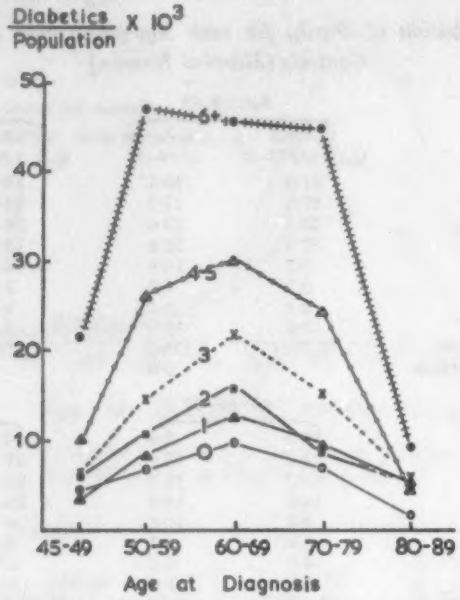

FIG. 5. The relative incidence of diabetes, by age, in married women of different parity.

parity. Compared with nulliparae, diabetes is about twice as common in women who have had three children, and six times as common in those who have had six or more. Diabetes is equally common in single women and nulliparous married women. The excess of women who develop diabetes is thus accounted for by those who have had three or more children.

Parity and age at diagnosis. Increasing parity does not lead to the appearance of diabetes at an earlier age. Table VIII shows the mean age at diagnosis in men and women aged more than 45. It was about 60 years for men, single women, and married women having fewer than three children. For women who had had three or more children there was, with increasing parity, a small but statistically significant increase in mean age at diagnosis. This increase can be accounted for by the fact, already discussed, that older women are likely to have had more children. Thus the mean age of all women over 45 admitted to the Queen Elizabeth Hospital rose with parity; in 1953 it was 58·4 in nulliparae, and 63·3 in those having seven or more children. The difference of 4·9 years compares with the difference of 3·9 years shown in Table VIII between nulliparous diabetics and those having seven or more children.

Age at childbirth in relation to onset of diabetes. Since increasing parity does not lead to an earlier onset of diabetes, does the mother's age at childbirth influence the time of onset of the disease? In 251 parous women now attending the Diabetic Clinic who were over 45 at the time diabetes was diagnosed, the

TABLE VIII

Mean Age at Diagnosis of Men, Single Women, and Married Women by Parity (aged over 45)

		Mean age (years)	*Standard error of mean*
Men		60·20	± 0·24
Women	Single	60·47	± 0·41
	Married: parity		
	0	60·0	± 0·45
	1	60·4	± 0·44
	2	60·7	± 0·41
	3	62·0	± 0·45
	4	62·5	± 0·54
	5	61·1	± 0·59
	6	64·2	± 0·70
	7+	63·9	± 0·42

TABLE IX

Effect of Mother's Age at Childbirth on Onset of Diabetes

Mean Age at Childbirth

Parity	*Number of cases*	*Mean age (years)*	*Standard error of mean*
1	39	28·66	± 0·66
2	56	29·10	± 0·59
3	50	28·64	± 0·58
4	30	28·30	± 0·81
5	32	28·80	± 0·52
6	15	30·87	± 0·32
7+	29	30·54	± 0·17

Age at Diagnosis of Diabetes

Mean age at childbirth (years)	*Age at diagnosis*		
	Under 60	*60 and over*	*Total*
Under 30	70	53	123
30 and over	43	41	84
Total	113	94	207

$\chi^2 = 0{\cdot}66$. With one degree of freedom this is not significant.

mother's age at the birth of each child was recorded, and the mean age of child-bearing determined. Table IX shows that, of the 207 women who had five children or less, the mean age at childbirth was independent of the number of the children, and thus can be considered in relationship to the age at diagnosis

of diabetes without regard to parity. The results are presented in the form of a χ^2 test, in which the patients are divided into those who developed diabetes before and after 60, and into those whose mean age at childbirth was under and over 30. We conclude that the mother's age at childbirth does not affect the age of onset of diabetes, because there was no significant excess of young mothers developing diabetes early.

Family history of diabetes and parity. Table X shows the percentage of married women giving a family history of diabetes, divided into four groups of increasing parity. Figures for men and single women are also shown, and the

TABLE X

Percentage Number of Cases with Positive Family History for each Parity Group

	Age at diagnosis (years)			
	45–59		*60–79*	
	Number of cases with known history	*% positive*	*Number of cases with known history*	*% positive*
Men	689	23·9	665	19·8
Single women	88	36·4	86	38·4
Married women by parity:				
All parities	906	32·5	1,285	24·0
Parity 0–1	240	37·5	271	29·9
,, 2–3	328	36·9	403	26·3
,, 4–5	168	28·0	266	22·6
,, 6+	170	21·2	345	17·7

$\chi^2 = 11{\cdot}41$ for the 45–59 age-group, which gives $P < 0{\cdot}01$, and 11·06 for the 60–79 age-group, giving $P < 0{\cdot}02$. This shows that there is a significant decrease in family history with increase in parity. There is also a significant difference between the two age-groups among married women.

TABLE XI

Weight in Relation to Parity in 276 Married Diabetic Women who were Aged between 50 and 54 at Diagnosis

Parity	*Number of patients*	*Mean weight as % of standard weight*	*Standard error of mean*	*% exceeding*	
				110% normal weight	*95th centile weight*
0	55	107	± 3·1	38	11
1	30	111	± 4·8	50	23
2	53	116	± 2·8	55	26
3	44	115	± 3·6	55	16
4	30	116	± 4·0	63	17
5 6	33	121	± 4·8	61	27
7+	31	124	± 4·6	74	35

patients are divided into those aged 45 to 59 and 60 to 79 at diagnosis of diabetes. The results show that, as parity increases, the proportion of patients with a family history of diabetes declines. Men give a family history less often than

women. Except in single women, the proportion of patients giving a family history also declines with age.

Parity and weight. In 276 diabetic women aged 50 to 54 we have made a separate record of height and weight at the time of diagnosis of diabetes (1949–58). Table XI shows the mean weight for the different parity groups, expressed as a percentage of the weight of healthy women of the same age and height (Kemsley, 1952). The Table also shows the percentage of women in each parity group exceeding 110 per cent. of the normal weight, and exceeding the 95th centile weight given in Kemsley's tables. On the average, diabetic women become slightly but progressively more obese with increasing parity.

Discussion

The age and sex specific incidence of diabetes can be calculated only by finding every diabetic in a community of known age and sex structure. The whole-population surveys in which this has been attempted have shown a clear preponderance of women aged over 50 (Wilkerson and Krall, 1947). This is in accord with the experience of all hospital clinics, even when the excess of elderly women in the general population is taken into account (Joslin, Dublin, and Marks, 1936; Harris, 1949; Munro, Eaton, and Glen, 1949; Pyke, 1956*a*). None of the whole-population surveys has been large or complete enough to show any difference between the sexes in younger age-groups. Although most of the series are rather small, some hospital clinics have noted an excess of men under 40 (Murray and Wang, 1956; Andrews, 1957; Vinke, Nagelsmit, van Buchem, and Smid, 1959; Traisman, Boehm, and Newcomb, 1959); but only Joslin, Dublin, and Marks (1936) and Dahlberg, Jorpes, Kallner, and Lichtenstein (1947) have substantiated this finding by taking into account the population at risk. Although figures taken from hospital clinics can never claim to be wholly representative of the true prevalence of diabetes, we know of no reason why our figures should not provide an accurate picture of the sex ratio of the disease below the age of 40. We have shown not only that diabetes is commoner in men than in women under 40 (Table III), but also that at all ages men are more commonly affected than nulliparous women, and than those who have borne one child (Table VII).

Mosenthal and Bolduan (1933) were the first to suspect that pregnancy might play a part in the development of diabetes. They noticed that the frequency with which diabetes was cited as a cause of death at ages over 45 was higher in married and widowed women than in single women. Joslin, Dublin, and Marks (1936) confirmed this conclusion, but attributed it to an association with obesity. Pyke (1956*a*) and Pyke and Please (1957) have denied that this is the whole explanation, because they found that the onset of diabetes was more common in women over 45 who are not obese than in men. They also pointed out that the increased incidence of obesity in parous diabetic women is not large enough to account for their excessive numbers in the diabetic population. Table XI

shows that at the time of diagnosis there is some increase in the weight of diabetic women with increasing parity, especially in those having seven or more children. While we agree that obesity is not likely to be the main factor in determining the high incidence of diabetes in multiparae, it is impossible to say more than this until control figures which show the relationship between weight and parity in the general population are available, and some allowance is made for the probable loss of weight before diabetes is diagnosed. Munro, Eaton, and Glen (1949) found that their excess of female patients was composed of married women over 40. They thought that this excess could be related, at least in part, to previous childbearing, because they found more mothers of large families among their patients than were expected. Pyke (1956*a*) analysed data from 955 diabetic patients, and found that the excess of female diabetics was confined to parous women. His original estimate that, compared with childless women, the chances of diabetes were increased threefold in women having five children and sevenfold in women having seven or more children, is in close agreement with our own (Table VII; Fig. 5). Pyke (1956*b*, 1957) later reduced this estimate, because he realized that by comparing the parity of all diabetic women over 45 with the parity of all women aged 45 to 49 in 1951 he had not allowed for the general decline in fertility of marriage since 1900 (Glass and Grebenik, 1954). He based his calculations, however, on the assumption that diabetes is equally common in both sexes below the age of 40. If, as we believe, the onset of diabetes is actually commoner in men below that age, he also erred in the opposite direction, and underestimated the effect of parity. Schweitzer (1958) also has found a connexion between the number of pregnancies and the incidence of diabetes. Although he found an equal incidence in men and nulliparous women, he estimated that the chances of diabetes developing are increased threefold in women having three to five children and fivefold in those having six or more. Vinke, Nagelsmit, van Buchem, and Smid (1599), on the other hand, could find no correlation between the incidences of diabetes and parity in a rather small series of 299 married women over 45 in 1956. Their control data show an extraordinarily high degree of parity, and it is possible that the diabetics and controls are not closely enough matched by age for their comparison to be valid. As an alternative to the hypothesis that pregnancy provokes diabetes, McConnell (1956) has suggested that women genetically disposed to the disease may also be more fecund than normal women. To support this view he pointed out that diabetes is a common disease, and recurrent mutation alone could not account for its estimated gene frequency of 15 per cent. He supposed that the diabetic gene might confer some biological advantage, to counter the loss from the population due to young diabetics failing to reproduce in the generations before insulin therapy. On the assumption that married nulliparae are likely to be less fecund than single women, he suggested comparing the incidence of diabetes in married nulliparae with its incidence in single women of the same age. We have done this (Table VII), and found that diabetes is equally common in the two groups, so that diabetes does not appear to be associated with an inherited high fertility.

In what way can the relationship between diabetes and parity be explained? The fact that a family history of diabetes is less common in highly multiparous women (Table X; Munro, Eaton, and Glen, 1949; Pyke, 1957) may mean that pregnancy can provoke diabetes in some women whose genetic tendency to the disease is not strong. This is in line with the simple idea suggested by the figures, that each pregnancy puts a 'load' on carbohydrate metabolism, and the greater the number of 'loads' the greater the tendency to diabetes. But if this were the whole explanation one would expect diabetes to appear at an earlier age in women who had had many children, and particularly in those who were young when their children were born. This is not so (Table IX); in fact, the mean age at diagnosis in all the groups we have considered is 60 (Table VIII; Munro, Eaton, and Glen, 1949; Pyke, 1956*a*), many years after childbearing is over. It is clear that, whatever the influence of parity, obesity, and inheritance, the mean age at which the disease becomes manifest varies hardly at all. Some precipitating factor associated with ageing must be invoked as determining the age at onset of the disease.

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Summary

1. The relative age and sex specific incidence of diabetes mellitus in Birmingham is shown for 5,441 patients who first attended the Diabetic Clinic between 1949 and 1958.

2. The onset of diabetes is commoner in men than women before the age of 40. After 40, as the incidence in both sexes increases, more women than men are affected. This difference is confined to married women, and diabetes remains commoner in men than in single women at all ages.

3. The number of live births in 2,318 married diabetic women of known ages over 45 is compared with those recorded in 7,608 married women of the same ages admitted to all departments of a general hospital. At all ages a greater percentage of the diabetic women have had four or more, and especially seven or more, children.

4. The incidence of diabetes increases with each increase in parity; compared with that in nulliparae, it is about twice as common in women who have had three children, and six times as common in those who have had six or more. It is equally common in single and married nulliparous women. After the age of 45, and allowing for the excess of elderly women in the population, the excess of women having the disease is accounted for by those who have borne three or more children.

5. We confirm the view that there is a small increase in weight with increasing parity, that the proportion of women with a family history of diabetes falls with increasing parity, and that the age at diagnosis of diabetes is uninfluenced by parity or by the mother's age at childbirth.

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PERNICIOUS ANAEMIA IN CHILDHOOD[1]

A report of Two Cases in One Family and their Relationship to the Aetiology of Pernicious Anaemia

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With Plates 12 and 13

The number of well documented cases of pernicious anaemia in childhood is very small. Reisner, Wolff, McKay, and Doyle, writing in 1951, reviewed the published reports and concluded that 16 patients, including the four they themselves reported, qualified for the diagnosis of juvenile pernicious anaemia. Their criteria for inclusion were macrocytic anaemia with megaloblastic marrow, exclusion of other causes of megaloblastic erythropoiesis, and the necessity for continued therapy to prevent relapse. Unfortunately the importance of latent forms of steatorrhoea was not known when many of these earlier reports were written, and a full fat-balance test was done in very few of the cases reviewed. The second criterion proposed for the diagnosis of pernicious anaemia was therefore not achieved by present-day standards. In the absence of a normal fat balance the certain diagnosis of pernicious anaemia in the earlier reports must therefore rest on some reasonably direct demonstration of intrinsic-factor deficiency. Before the introduction of labelled vitamin B_{12} such evidence could be provided in two ways. First, by showing that the patient's gastric juice, after incubation with minced beef or with small quantities of fresh liver, failed to induce reticulocytosis when administered orally to another patient suffering from untreated pernicious anaemia; secondly, by demonstrating a reticulocytosis after the patient had received oral vitamin B_{12} with intrinsic factor, oral administration of the vitamin alone having been found ineffective. The second method of demonstrating intrinsic factor deficiency can, however, be accepted only after careful scrutiny of the detailed evidence. Callender and Evans (1955) have shown that, although the quantity of intrinsic factor necessary to induce absorption of vitamin B_{12} in patients with pernicious anaemia is ineffective in patients with steatorrhoea, administration of a larger amount of intrinsic factor will in fact enhance absorption in these patients. Only four of the earlier reports fulfil the present criteria for diagnosis.

In recent years three patients with juvenile pernicious anaemia have been fully investigated by modern techniques using labelled vitamin B_{12} to establish

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the diagnosis (Mollin, Baker, and Doniach, 1955; Stevenson, Little, and Langley, 1956; Harris-Jones, Swan, and Tudhope, 1957). Mollin, Baker, and Doniach's patient had been previously described in infancy by Langmead and Doniach (1937). The sibs described here are the fourth and fifth patients to be investigated in this way, and bring the number of proven cases of juvenile pernicious anaemia to nine. Some of the main features of these nine cases are summarized in the Table.

Case Histories

First child, A. W., born 18.11.52

Pregnancy and delivery were uneventful, and the birth weight 3·34 kg. The parents were unrelated. A. W. was the first child of the mother's second marriage. Two younger siblings were born of the same marriage, R. W. and J. W., and two healthy children had been born of the first marriage.

First admission. A. W. was first seen at the age of eight months (July 1953), when she was admitted to University College Hospital with a history of failure to thrive since birth. Stools had been intermittently loose from the age of three to six months, and vomiting had been associated with respiratory infection for several days before admission. Social conditions were poor, welfare clinics unattended, and feeding erratic. After two weeks of breast-feeding she had been fed with dilute sweetened condensed milk for three months, followed by No. 1 'Ostermilk', and later Full-Cream National Dried Milk from the age of six months. Supplements of ascorbic acid, 15 mg. daily, had been given from three to six months, and mashed potatoes were introduced at seven months.

On examination she was slightly pale and very wasted, weighing only 5·35 kg. (< 3 percentile, 2·27 kg. less than her expected weight). No other clinical abnormality was found. The central nervous system was normal. A blood count showed an initial haemoglobin level of 14 g. per 100 ml., falling a week later to 10·9 g. per 100 ml., initial red-cell count 3,100,000 per cu. mm., reticulocytes 2·1 per cent., mean corpuscular diameter 7·7 to 7·9 μ, mean corpuscular haemoglobin concentration 30 per cent., and mean corpuscular volume 100 cu. μ. The red-cell fragility and electrophoresis of haemoglobin were normal. The white-cell and differential counts were normal. A marrow smear showed 10·5 per cent. megaloblasts, but was otherwise normal. The urine showed no abnormality, and normal results were obtained for serum calcium and inorganic phosphate, blood urea, and plasma electrolytes. Chest X-rays were normal. There was no radiological evidence of rickets, but the wrist showed ossification of only one carpal centre, corresponding to a bone age of two to three months. A histamine test meal yielded free acid, and a stool showed normal tryptic activity.

She was thought to be suffering from megaloblastic anaemia of infancy of nutritional origin, and was treated with folic acid intramuscularly and later orally, with supplements of ferrous sulphate and ascorbic acid. There was an excellent response, with immediate improvement of appetite, rapid gain of weight, a reticulocytosis of 17 per cent., an increase of haemoglobin to 13·5 g. per 100 ml., and restoration to normoblastic marrow after eight days' treatment. She was discharged at nine and a half months, weighing 7·34 kg. (just under the 3 percentile); the red cells were 4,000,000 per cu. mm., haemoglobin 13·5 g. per 100 ml., mean corpuscular diameter 7·4 μ, and mean corpuscular haemoglobin concentration 34 per cent. The folic acid was discontinued after a total

Some Clinical and Laboratory Findings in Nine Patients with Juvenile Pernicious Anaemia

Author	*Patient*		*Tongue*	*Central nervous system*	*Physical development*	*Mental development*	*Family history*
	Sex	*Age when first anaemic (years)*					
Pohl (1940)	F	13	Smooth	Normal	..	Normal for age	One sister aged 7, well
Benjamin (1948)	F	1 4/12	Pale, atrophic	Normal	Growth stopped in initial illness and in worst relapse. Grey hair at 8 years	..	Older sib died aged 21 months after an illness similar to the patient's
Reisner, Wolff, McKay, and Doyle (1951)	(C. Z.) F	2	Recurrent atrophic glossitis	Absent leg reflexes and diminished vibration sense initially	Well developed and nourished	..	Sib of V. Z.
Reisner and Ellsworth (1955)	(V. Z.) F	8	Smooth, red	Normal at first. Absent deep reflexes in relapse	Well developed and nourished	..	Sib of C. Z.
Mollin, Baker, and Doniach (1955)	M	1 4/12	Normal	Normal	At 18 years small and sexually under-developed	Slightly retarded	Parents first cousins. Father developed classical pernicious anaemia
Stevenson, Little, and Langley (1956)	M	2 4/12	Smooth	Normal	Height lower percentile. Rapid gain in weight after B_{12}	..	No consanguinity. Mother and brother had normal serum B_{12}
Harris-Jones, Swan, and Tudhope (1957)	F	16	Sore	Normal	Normal height and build	..	None. No consanguinity
Present report	(A. W.) F	4/12	Normal	Normal	Poorly developed. Growth spurt after vitamin B_{12}	I.Q. 88 at 6 4/12 years	Sib of R. W.
Present report	(R. W.) M	4/12	Normal	Normal	Poorly developed. Growth spurt after vitamin B_{12}	Retarded when diagnosed, now making good progress	Sib of A. W.

Author	*Bone marrow*	*Treatment*	*Reticulocytes after treatment (%)*	*Gastric secretion*		*Gastric biopsy*	*Small-intestinal function*
				Acid	*Pepsin*		
Pohl (1940)	Not done	Liver	36·5	Histamine-resistant achlorhydria	..	..	Barium follow-through normal
Benjamin (1948)	Megaloblastic	Liver	42	Acid absent initially, present later	..	..	Barium follow-through, glucose tolerance, fat balance (96%), all normal
Reisner, Wolff, McKay, and Doyle (1951)	Megaloblastic	B_{12} injections	26	Histamine-resistant achlorhydria at first; free acid after treatment. Acid again absent in relapse	..	..	..
Reisner and Ellsworth (1955)	Megaloblastic	B_{12} injections	16·4	Hypochlorhydria before histamine	..	..	..
Mollin, Baker, and Doniach (1955)	Megaloblastic	Treated when only slightly B_{12}-deficient	..	Normal. 90% free acid after histamine	Present	Normal	Barium follow-through, glucose tolerance, vitamin-A absorption, fat balance (96%), all normal
Stevenson, Little, and Langley (1956)	Megaloblastic	B_{12} injections	48	Normal	Present	..	Barium follow-through, glucose tolerance, vitamin-A absorption, all normal
Harris-Jones, Swan, and Tudhope (1957)	Megaloblastic	B_{12} injections	20	Normal	Present	Normal	Fat absorption normal (92%). No malabsorption of folic acid
Present report (A. W.)	Megaloblastic	B_{12} injections	22	Normal	Uropepsin present in urine	Normal	Barium follow-through normal. Fat absorption normal (92·5%, 90%). Duodenal biopsy normal
Present report (R. W.)	Megaloblastic	B_{12} injections	20	Normal	Uropepsin present in urine	Subtotal gastric atrophy	Barium follow-through normal. Fat absorption, see case report. Jejunal biopsy normal

dose of 400 mg., but she continued treatment with ferrous sulphate and ascorbic acid supplements as an out-patient.

Second admission. As an out-patient the child became increasingly difficult to feed, especially with solids, and four months later (4.1.54), at the age of 13½ months, she was readmitted in relapse, weighing only 6·35 kg. Her abdomen was prominent and she was slightly wasted, but the spleen was not palpable. No other abnormality except pallor was noticed; there was no evidence of infection. The central nervous system was normal. The haemoglobin was 6·9 g. per 100 ml., red cells 2,100,000 per cu. mm., mean corpuscular diameter 7·5 μ, mean corpuscular haemoglobin concentration 35 per cent., mean corpuscular volume 96 cu. μ, and reticulocytes 1·5 per cent. The marrow was normally cellular, and showed 22 per cent. megaloblasts. The plasma bilirubin was 0·4 mg. per 100 ml. This relapse was treated with intramuscular vitamin B_{12}. Supplements of ascorbic acid and ferrous sulphate were continued. A reticulocytosis of 12·5 per cent. occurred on the fourth day of treatment, and within three weeks the haemoglobin had increased to 13·0 g. per 100 ml. and she had gained 1·36 kg. in weight (3 percentile). Four weeks after the start of B_{12} therapy the marrow puncture was repeated, and the smear was found to be normal. The vitamin B_{12} was discontinued after a total dose of 900 μg.

Third admission. In July 1957, aged four years and seven months, A. W. was seen again with a two months' history of anorexia, lack of energy, misery, and loss of weight. She had reverted to baby talk. On examination she was small in height (96 cm. (3 percentile); upper segment 55 cm., lower segment 40·5 cm.; upper/lower segment ratio increased). Her weight was 15·4 kg. (25 percentile). Her abdomen was prominent, and there was obvious pallor, tachycardia, and cardiac enlargement with a grade 2 systolic murmur and venous hum. The tongue was smooth. The spleen was not palpable, but the liver extended 3 to 5 cm. below the costal margin. No abnormality was detected in the central nervous system apart from her infantile behaviour. The haemoglobin was 5·6 g. per 100 ml., red cells 1,400,000 per cu. mm., mean corpuscular diameter 7·7 μ, mean corpuscular haemoglobin concentration 38 per cent., mean corpuscular volume 103 cu. μ, and reticulocytes 1·8 per cent. The marrow smear showed 42 per cent. megaloblasts. A histamine test meal showed free HCl secretion. Ascorbic-acid saturation, vitamin-A absorption, and glucose tolerance were all normal. A five-day fat balance on a standard fat intake showed 92·5 per cent. absorption. No giardia, ova, or cysts were found in a stool. A barium meal and follow-through gave normal results. Bone age was assessed on X-rays of the carpus at one year. The blood cholesterol was 163 mg. per 100 ml.

No radiocobalt-labelled vitamin B_{12} was available at this time, and, although pernicious anaemia was now considered to be the likely diagnosis, treatment could not be withheld, and further investigation was therefore postponed. A second course of intramuscular vitamin B_{12}, in a total dose of 290 μg., was given over 17 days, but was not continued after the child's discharge. She responded with a return of energy, appetite, and normal speech, and by rapid gain of weight. There was a reticulocytosis of 22 per cent. on the 11th day of treatment, followed by a rise in the haemoglobin level to 13·5 g. per 100 ml. and the return to normocytic marrow after three weeks.

Fourth admission. A. W. remained well after her discharge, and was readmitted with her brother for radioactive studies in May 1959, aged six and a half years. Mental and physical progress had been well maintained, but her abdomen remained prominent, her stature short (110 cm.; 10 percentile), and weight

21 kg. (37 percentile). She is now maintained on regular injections of vitamin B_{12}.

Milestones and previous illnesses. A. W. stood alone at 17 months, and walked at 21 months; she fed herself from 19 months, and became clean and dry between the ages of two and three years. Speech was delayed, and she said her first words with meaning at 20 months, and put words together in sentences only at three years. She reverted in speech and behaviour to infancy during her second relapse at four and a half years, but improved subsequently. The intelligence quotient assessed at six years and eight months was 88 on the revised Stanford-Binet scale. Apart from the episodes of megaloblastic anaemia, she had had febrile convulsions when aged two and a half years, and her tonsils were removed at four years.

Routine investigations on the fourth admission. The haemoglobin was 13·5 g. per 100 ml., red cells 4,100,000 per cu. mm., mean corpuscular diameter 7·4 μ, mean corpuscular haemoglobin concentration 36 per cent., and mean corpuscular volume 8·7 cu. μ; white cells 10,000 per cu. mm., with a normal differential count; and platelets 390,000 per cu. mm. A marrow smear showed 38 per cent. megaloblasts. A five-day fat balance showed 96 per cent. fat absorption. Radiological assessment of bone age (wrist and elbow) was four to five years. The electroencephalogram was within normal limits for the age. Serum vitamin B_{12} was 60 $\mu\mu$g. per ml. (normal 140 to 900 $\mu\mu$g. per ml.). Chromatography of the urine and plasma for amino acids gave a normal result.

Gastric investigations on the fourth admission. Fasting gastric juice contained free acid 1·2 ml., and total acid = 1·3 ml. of N/10 acid per 100 ml. The urine contained 19·5 units of uropepsin in 24 hours. A gastric mucosal biopsy carried out by Dr. Margot Shiner is shown in Plate 12, Fig. 6. A duodenal biopsy (obtained after two unsuccessful attempts at jejunal biopsy) is shown in Plate 12, Fig. 7. The gastric biopsy showed the full thickness of the mucosa with the muscularis mucosae. The mucosa was normal, with a full complement of oxyntic and pepsinogen cells; there was no inflammation, fibrosis or atrophy. The duodenum showed a normal mucosa and villi, except for one focus of abnormal lymphocytic infiltration in the muscularis mucosae.

Second child, R. W., born 23.1.58

The second child of the same parents was born at home normally after an uneventful pregnancy; his birth weight was 3·34 kg. He was fed with sweetened condensed milk, and solids, including cereals, were introduced at six months; he thrived until nine months (October 1958), when he had a mild attack of gastroenteritis. He attended another hospital then for the first time, and was treated as an out-patient with terramycin and oral glucose saline, with improvement. He did not, however, regain his normal equanimity, and was difficult to manage. He was next seen at hospital in January 1959, aged 11 months, with otitis media, and weighing 8·8 kg. The diagnosis of coeliac disease was considered, but he was so miserable that an attempted stool collection was abandoned, and he was discharged four days later, having gained 114 g. in weight. The haemoglobin was 9·8 g. per 100 ml., and there was an iron-deficiency anaemia with occasional macrocytosis. He was readmitted three days later, weighing 8·4 kg., with a paraphimosis, and on this occasion further tests were made. Stool trypsin was present at a dilution of 1/100, and the finger-print test for sweat chloride content was normal. A three-day fat balance showed an average of 75 per cent. absorption. The daily variation, however, was very great, absorption being approximately 55 per cent., 85 per cent., and 90 per

cent. Vitamin-A absorption was normal. The haemoglobin was 9·1 g. per 100 ml., and white cells 9,000 per cu. mm., with a normal differential count. The radiological bone age was six months. A gluten-free diet was started on 27.1.59. It was taken well, and his weight had risen to 8·9 kg. on his discharge at 13 months. While in hospital he developed a large facial abscess, and later measles. He was given sulphadimidine.

As an out-patient he was treated for bronchitis with terramycin, and a gluten-free diet and oral iron were continued. In spite of this his weight was only 8·25 kg. when he was readmitted in March 1959, aged 14 months, with bronchopneumonia, and the haemoglobin level had fallen to 8 g. per 100 ml. Further investigation of the anaemia showed a mean corpuscular volume of 110 cu.μ, mean corpuscular haemoglobin concentration 31·6 per cent., and reticulocytes 1·5 per cent.; later the haemoglobin was 6·95 g. per 100 ml., with macrocytosis. A marrow smear on 23.4.59 (at the age of 15 months) was megaloblastic.

He was transferred to University College Hospital on 25.4.59, aged 15 months, his weight being 7·7 kg. (3 percentile), and height 75 cm. (< 3 percentile). He was pale, and showed many of the classical features of coeliac disease. He was constantly miserable, and had no interest in food, although maintained on a gluten-free diet. There was generalized wasting, accentuating his abdominal distension. The liver edge was palpable at the costal margin, but the spleen was not felt. The tongue was smooth. There was generalized mild lymphadenopathy, and on the day following admission he developed a purpuric rash on the legs. He appeared retarded in mental development. He was able to sit, though he preferred to lie, and made no attempt to pull himself up. He made noises, but no words. He was neither dry nor clean. It was originally thought that he had failed to respond to the gluten-free diet because of frequent infections resulting from his prolonged anaemia. It was therefore decided to investigate and treat the anaemia before further study of the 'coeliac syndrome' was made. The results (Figs. 1 and 2) showed conclusively that he was suffering from pernicious anaemia, and treatment with intramuscular vitamin B_{12} was begun.

This treatment produced a striking result. From the day of his initial injection his temperament improved, his appetite increased, and his weight, which had been stationary, rose rapidly. He began to sit voluntarily, and later to pull himself up. A reticulocytosis occurred on the fifth day of treatment, but there was no significant increase in haemoglobin until two weeks of treatment had been given, after which its level rose steadily. A marrow smear was normal after a total dosage of 750 μg. vitamin B_{12} had been given in six weeks. His weight was then 11·3 kg. (10 percentile) and his height 76 cm. (3 percentile). Five weeks after the start of treatment a normal diet, containing gluten and of constant fat content, was introduced, and after stabilization on this diet for one week a five-day fat balance was carried out, and was normal. This test was completed without difficulty because of the child's improved appetite, and the introduction of gluten caused no set-back in growth or behaviour. His stay in hospital was complicated by an attack of acute bronchitis, treated with tetracycline, and later by streptococcal tonsillitis, treated with penicillin.

He was discharged at 17½ months, on a normal diet, happy, and easily managed. He is now maintained on regular doses of vitamin B_{12}. His progress after discharge was interrupted only by two mild attacks of otitis media, which responded rapidly to antibiotics. By 18½ months he was walking alone, and increasing his vocabulary. At 22 months he weighed 12·9 kg. (< 75 percentile), his height was 81 cm. (< 10 percentile), and the haemoglobin 16·1 g. per 100 ml.

Routine haematological investigations. On 5.5.59 the haemoglobin was 7·4 g. per 100 ml., red cells 2,200,000 per cu.mm., white cells 7,800 per cu.mm. (neutrophils 12 per cent., lymphocytes 89 per cent., monocytes 4 per cent.), reticulocytes 2 per cent., mean corpuscular diameter 8·1 μ, mean corpuscular haemoglobin concentration 37 per cent., mean corpuscular volume 93 cu.μ, and platelets 60,000 to 140,000 per cu.mm. Prothrombin concentration was 100 per cent. of normal. Serum vitamin B_{12} was 30 $\mu\mu$g. per ml. (normal 140 to 900 $\mu\mu$g. per ml.). Five days after starting vitamin B_{12} reticulocytes were 20 per cent. Six weeks after starting vitamin B_{12} the haemoglobin was 14·0 g. per 100 ml., and the mean corpuscular diameter 7·1 μ; a bone-marrow smear was normal.

Other investigations. A histamine test meal showed a normal amount of free acid. The urine was normal on routine examination and on chromatography for amino acids. The plasma contained protein 6·4 g. (albumin 4·2 g., globulin 2·2 g.) per 100 ml.; chromatography for amino acids, and an electrophoretic strip, gave normal results. The blood cholesterol was 125 mg. per 100 ml. A glucose-tolerance test (14·3 g. by mouth) showed a rise from 85 mg. to 115 mg. per 100 ml. in the first half-hour. The results of a barium meal and follow-through were normal. A fat-balance test after six weeks' treatment with vitamin B_{12} and a normal diet showed 92 per cent. absorption. X-rays of the bones showed considerably retarded ossification. Urinary uropepsin was 10·5 units per 100 ml.

Gastric biopsy showed the full thickness of the mucosa with the muscularis mucosae. The mucosa was thin, and the glands reduced to about half the normal number. They were all mucoid in type, and were separated by a non-inflamed cellular fibrous stroma. The diagnosis was subtotal gastric atrophy (Plate 13, Fig. 8). Attempted jejunal biopsy showed fragments of mucosa, most of which was gastric. There were a few broken-up mucosal strips which resembled small-intestinal villi, and in one area a few glands and surrounding lamina propria of small intestine. These fragments of jejunal mucosa and villi appeared healthy, and showed none of the villous atrophy and glandular hyperplasia seen in coeliac disease.

A third child, J. W., was born at home after a normal pregnancy and delivery on 26.5.59, weighing 3·34 kg. At three months she was making normal progress, and there were no clinical abnormalities. *Investigations.* The haemoglobin was 13·5 g. per 100 ml., mean corpuscular diameter 7·1 μ, and white cells 12,000 per cu.mm. with a normal differential count. The serum vitamin B_{12} was 100 $\mu\mu$g. per ml. (normal 140 to 900 $\mu\mu$g. per ml.). At five months the haemoglobin was 14·5 g. per 100 ml. and mean corpuscular diameter 7·0 μ.

Both parents were healthy, with normal blood counts and free acid shown on the azure A test without histamine. The father had 104 units of uropepsin in the 24 hours' urine, and the mother 59 units.

Studies with Radioactive Vitamin B_{12}

Methods

^{58}Co-labelled vitamin B_{12} was obtained freeze-dried from the Radiochemical Centre. It was dissolved in water immediately before use, and all studies were made with freshly prepared material. A suitable quantity of vitamin was given

by mouth to the patients fasting, and when it was given with a source of intrinsic factor the two were mixed 15 minutes before administration. Counting was performed with a surface scintillation counter, measurements being made over the centre of the anterior surface projection of the liver and over the lower

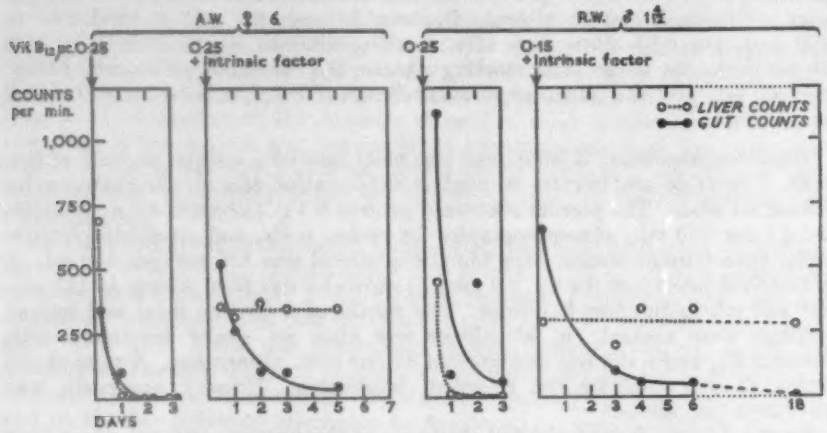

FIG. 1. Hepatic and lower abdominal counts in A. W. and R. W. after doses of ^{58}Co-labelled vitamin in B_{12} with and without a source of intrinsic factor.

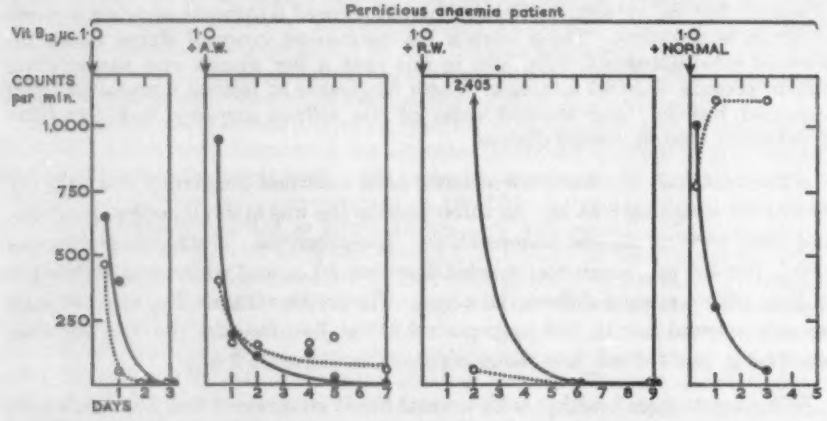

FIG. 2. Hepatic and lower abdominal counts in a patient with pernicious anaemia after oral doses of ^{58}Co-labelled vitamin B_{12} given with and without samples of gastric juice from A. W., R. W., and a normal subject.

abdomen. Counting was continued to a total of 1,000 counts. This method can be calibrated to give reasonable quantitative results of absorption in adults (Lambert and Prankerd, unpublished data), but in children the size of the liver is too variable to permit accurate measurement of uptake. Counting was continued until no radioactivity was detectable over the lower abdomen.

Results (Figs. 1 and 2)

A. W. After oral administration of 0·25 μc of ^{58}Co-labelled vitamin B_{12}, no hepatic uptake could be shown, the liver counts falling to background levels within two days in parallel with the intestinal counts. When the same dose was given mixed with 2 g. of crude intrinsic factor ('pepsac', Boots Ltd.) the vitamin

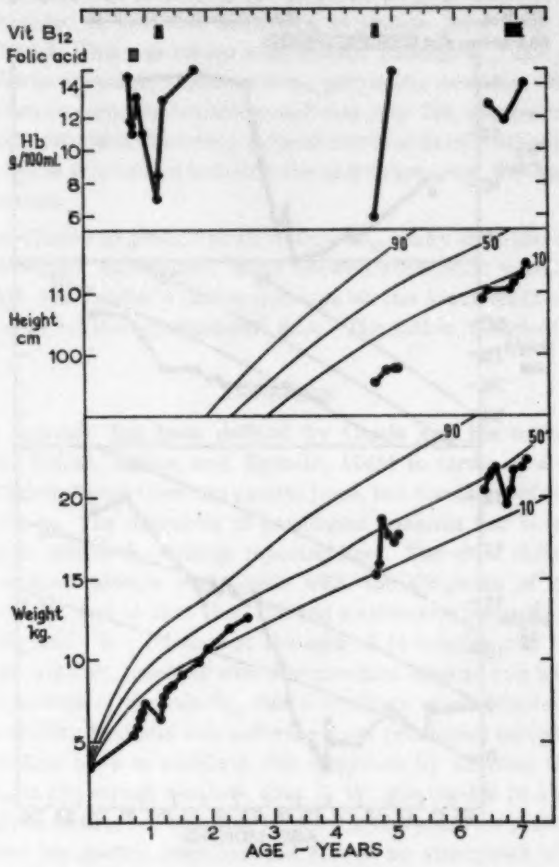

FIG. 3. Haemoglobin estimations and height and weight charts of A. W. in relation to therapy. The thin lines show the percentage incidence in the population of height and weight below the line levels.

B_{12} was absorbed, and hepatic counts remained high after the bowel had emptied. Finally, the absence of intrinsic factor from A. W.'s gastric juice was shown by its failure to induce more than a very slight degree of absorption of vitamin B_{12} in a patient with pernicious anaemia. A three-hour collection of gastric juice from A. W. yielded 25 ml. This was mixed with 1 μc of vitamin B_{12}, and 30 minutes later the mixture was administered by gastric tube to a patient with

known pernicious anaemia. Only a slight degree of hepatic radioactivity could be recorded after seven days, representing an absorption of less than 10 per cent. This compares with 45 per cent. absorption after administration of the same dose of vitamin B_{12} mixed with 25 ml. of gastric juice from a normal subject.

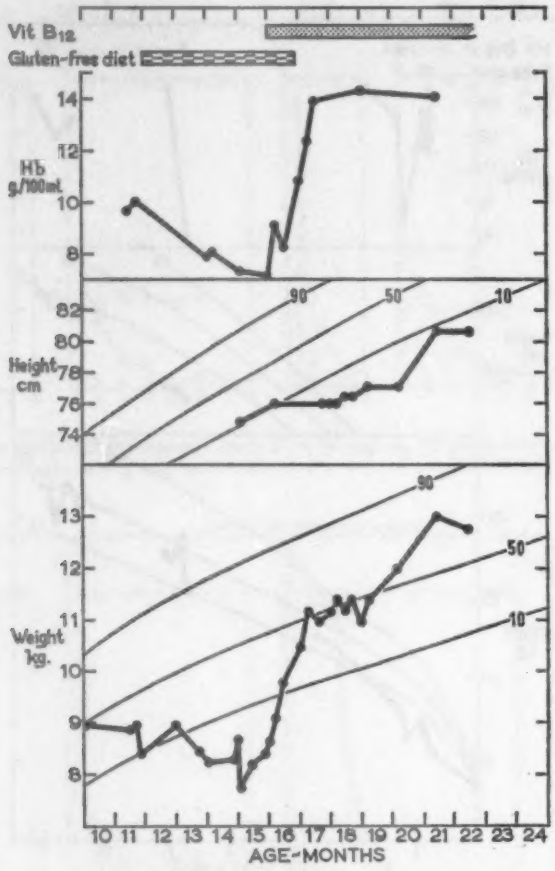

FIG. 4. Haemoglobin estimations and height and weight charts of R. W. in relation to therapy. The thin lines show the percentage incidence in the population of height and weight below the line levels.

R. W. Similar results were obtained. No evidence of absorption was obtained after the oral administration of 0·25 μc vitamin B_{12}, but good absorption was recorded after oral administration of 0·15 μc vitamin B_{12} mixed with intrinsic factor (2 g. 'pepsac'). A two-hour collection from R. W. yielded only 10 ml. of gastric juice. This, mixed with 1 μc vitamin B_{12}, failed to induce any absorption of the vitamin when given by gastric tube to a patient with pernicious anaemia.

These findings are summarized in Figs. 1 and 2. In both children the oral administration of labelled vitamin B_{12} for these tests was always preceded by the subcutaneous injection of a suitable dose of carbamylcholine chloride ('carbachol') (Mollin, 1959), which has been shown to stimulate the maximum secretion of intrinsic factor.

J. W. This infant was tested for her ability to secrete intrinsic factor at the age of five months. A two-hour collection of gastric juice from her stomach yielded only 10 ml. This was mixed with 1 μc of vitamin B_{12}, and administered by gastric tube to a patient suffering from pernicious anaemia. When the gut counts had fallen to zero, the hepatic count was only 173, representing a negligible absorption. No data regarding normal intrinsic-factor activity in infancy are available, but it is intended to follow the child's progress, lest she too develop pernicious anaemia.

The parents. Each was given 1 μc of vitamin B_{12} orally after the subcutaneous injection of 0·25 mg. 'carbachol'. Both showed absorption within the normal range, although the mother's absorption was at the lower limit of this range, being 24 per cent. of the administered dose. The father absorbed 41 per cent. of his dose.

Discussion

Pernicious anaemia has been defined by Castle and his colleagues (Berk, Castle, Welch, Heinle, Anker, and Epstein, 1948) in terms of a deficiency or absence of intrinsic factor from the gastric juice, but the cause of this deficiency remains unknown. The diagnosis of pernicious anaemia has been established beyond doubt in two of the siblings reported here. The elder child, A. W., first presented a clinical picture compatible with the diagnosis of megaloblastic anaemia of infancy, and at that time showed a reticulocytosis after the administration of folic acid. Her relapses at the ages of 14 months and four years, on an adequate mixed diet, together with her excellent clinical and haematological response to injections of vitamin B_{12}, threw doubt on the original diagnosis, and raised the possibility that she was suffering from pernicious anaemia. The present investigations have established this diagnosis by showing that the level of vitamin B_{12} in the serum was low, that A. W. was unable to absorb labelled vitamin B_{12} given orally, but was able to do so in the presence of intrinsic factor, and finally that her gastric juice induced almost no absorption of vitamin B_{12} from the gut of a patient with known pernicious anaemia. It has been shown (Mollin, Baker, and Doniach, 1955) that the deficiency of intrinsic factor in patients with pernicious anaemia may not be complete. Furthermore, no other cause of megaloblastic anaemia in A. W. could be invoked, since her fat-balance and barium follow-through findings were both normal.

The evidence that the younger sib, R. W., has pernicious anaemia is equally unequivocal, but in him the initial clinical features were more complex. He showed on clinical examination all the features of coeliac disease, and a fat-balance test over a three-day period showed an absorption of 75 per cent., tending to confirm this diagnosis. It should be emphasized, however, that the

daily quantities of faecal fat over this period were somewhat variable. A longer test period at this stage would have been desirable, but this could not be undertaken because of the child's poor appetite and general condition. His megaloblastic anaemia could obviously have been attributable to coeliac disease, but investigation has shown that, like his sister, he is suffering from pernicious anaemia. He failed to absorb orally administered vitamin B_{12}, but was able to do so in the presence of intrinsic factor, and his own gastric juice was totally unable to induce absorption of labelled vitamin B_{12} in a subject with known pernicious anaemia. His response to treatment was of great interest. Having failed completely to show any clinical or haematological response to a gluten-free diet, he showed an immediate improvement in temper and appetite as soon as injections of vitamin B_{12} were started. After five weeks of treatment, when his haemoglobin was nearing a normal value and his clinical improvement was most satisfactory, the gluten-free diet was discontinued without subsequent relapse. A five-day fat-balance test on a normal diet then showed an absorption of 92·2 per cent. A jejunal biopsy gave a normal result, but gastric biopsy showed some degree of atrophy. It must be concluded that the clinical features of the coeliac syndrome, and perhaps even an actual malabsorption of fat, had been produced in this child by a combination of pernicious anaemia with other factors, possibly with the repeated infections from which he had suffered.

Pernicious Anaemia in Childhood

The rarity of pernicious anaemia in childhood has been stressed. Although rare, its occurrence is important because its study throws some light on the pathogenesis of the disease. Of especial interest are the familial incidence, the relationship between the production of acid and that of intrinsic factor, the effect of intrinsic factor on physical growth, and its possible effect on intestinal absorption. We shall here review the nine proved cases in an attempt to characterize the disease, and to define its relationship with the classical form of pernicious anaemia as seen in the middle-aged and elderly. Not included in the group of nine patients are three children, in each of whom the features of idiopathic hypoparathyroidism were combined with those of a megaloblastic anaemia, probably pernicious in type (Reisner and Ellsworth, 1955; Hurwitz, 1956; McIntyre, Hahn, Conley, and Glass, 1959). In two of these cases the diagnosis of pernicious anaemia is not completely certain, in one because no fat-balance test was done, and in the other because the patient had received phenytoin sodium, and might have developed a megaloblastic anaemia from this cause. Nevertheless, the probable coexistence of two such rare diseases in three patients deserves mention; no hypothesis which could account for such an association has yet been offered.

Clinical features. Of the nine children six were girls and three boys. They were first found to be anaemic at ages ranging from eight months to 16 years. The symptoms leading to their investigation were not especially noteworthy; the only common symptoms apart from those of anaemia were gastrointestinal,

and several of the patients gave a history of anorexia, vomiting, and diarrhoea. One patient complained of a sore tongue, and five others showed abnormalities of the tongue on examination; in two the tongues were described as smooth, in one as smooth and red, and in one as pale and atrophic; the fifth (Reisner, Wolff, McKay, and Doyle's patient C. Z.) suffered recurrent attacks of atrophic glossitis. Seven of the patients showed no abnormality in the nervous system; one had absent reflexes and diminished vibration sense in the legs, and these abnormal signs disappeared after treatment. Another patient had no abnormalities in the nervous system when first seen, but showed diminution of tendon reflexes during a relapse. Complications in the nervous system have been described in several other patients reported to have juvenile pernicious anaemia, but who are not acceptable on the present strict criteria. The second pair of sibs reported by Reisner, Wolff, McKay, and Doyle (1951) both showed absent ankle jerks and extensor plantar responses, as well as mental retardation. Deficiency of intrinsic factor was not, however, demonstrated directly in these children.

Family history. The familial incidence of pernicious anaemia in childhood is striking. Included in the nine cases are two pairs of sibs; in neither family were the parents related. The second pair of sibs reported by Reisner, Wolff, McKay, and Doyle, mentioned above and not acceptable on the present criteria, had grandparents who were first cousins. The parents of the patient of Mollin, Baker, and Doniach were first cousins, and the father was found to have classical pernicious anaemia in middle age. Benjamin's patient had an older sib who died, aged 21 months, after an illness very similar to that of the patient (Benjamin, 1948). This high familial incidence contrasts with the definite but very much lower tendency for classical pernicious anaemia to be found in relatives of patients suffering from the disease. Recent work (McIntyre, Hahn, Conley, and Glass, 1959) has shown that relatives of patients with pernicious anaemia have a significantly reduced ability to absorb vitamin B_{12}, even in the absence of anaemia or achlorhydria. It is interesting that the affected children we have studied are of the second marriage of one parent, whose children by her first marriage were normal.

Gastric function. Juvenile pernicious anaemia shows its most striking contrast to the classical form in the relationship between intrinsic-factor secretion and that of acid and pepsin in the stomach. In classical pernicious anaemia achlorhydria is an almost invariable feature, and only very rarely (Murphy, 1948; Beebe and Wintrobe, 1933) has absence of intrinsic factor been recorded in a patient with free gastric acid. It is, of course, known that achlorhydria may precede the clinical manifestations of pernicious anaemia. Studies with labelled vitamin B_{12} have shown that most non-anaemic patients with atrophic gastritis absorb vitamin B_{12} normally (Mollin, 1959), but that 12 per cent. of these patients absorb as little vitamin B_{12} as patients with pernicious anaemia. This suggests that gastric atrophy may progress in stages culminating in loss of intrinsic factor, and this sort of progression has in fact been observed (Mollin,

Booth, and Baker, 1957). Complete gastric atrophy may, however, long precede the development of pernicious anaemia (Robertson, Wood, and Joske, 1955). These observations apply to patients with no family history of pernicious anaemia, but the same sequence probably occurs in patients in whose families the disease has already appeared. Callender and Denborough (1957) showed that histological changes were found in the gastric mucosa in some relatives of patients who had pernicious anaemia with achlorhydria, but these relatives had no impairment of secretion of intrinsic factor or pepsin, and had normal serum levels of vitamin B_{12}. Moreover, patients with proved pernicious anaemia have no pepsin in the gastric juice, and low blood-pepsin levels (Farnsworth, Speer, and Alt, 1946). All these observations suggest that, whatever the exact pathogenesis, the loss of intrinsic factor in pernicious anaemia in adults is a consequence of a severe degree of gastric atrophy, and this view is supported by the atrophic gastritis commonly found on biopsy or autopsy. In sharp contrast, the patients who have developed pernicious anaemia in childhood show clearly that loss of intrinsic factor may be an isolated defect, occurring in a stomach which is histologically normal and which is secreting acid and pepsin in normal quantities. Several patients have further shown the interesting phenomenon of temporary loss of acid secretion during relapse of their anaemia. Of the nine patients under discussion, only one (Pohl, 1940) had histamine-fast achlorhydria, but in this patient no bone-marrow was examined or fat balance reported. All the others showed free acid on some occasions. Four patients (Stevenson, Little, and Langley, 1956; Harris-Jones, Swan, and Tudhope, 1957; and both children in the present report) had free acid in normal amounts. In Benjamin's (1948) patient acid was absent initially, but present later after treatment of the anaemia. Mollin, Baker, and Doniach's (1955) patient had no free acid when seen first at 13 months, but normal acid secretion when the complete study was carried out at the age of 18 years. Of the sibs C. Z. and V. Z. (Reisner, Wolff, McKay, and Doyle, 1951; Reisner and Ellsworth, 1955) one had histamine-fast achlorhydria when first seen, free acid after treatment, and achlorhydria again during a relapse, and the other had hypochlorhydria before histamine. Gastric secretion of pepsin was estimated in three patients, and was normal in all of them. Uropepsin levels were estimated in A. W. and R. W., and were within the normal range, although in A. W.'s urine the amounts were small. Gastric biopsy was done in four patients; in three the sections were completely normal (Mollin, Baker, and Doniach, 1955; Harris-Jones, Swan, and Tudhope, 1957; our patient A. W.), while that taken from R. W. showed a moderate degree of atrophy.

The pathogenesis of pernicious anaemia. These results show that children with pernicious anaemia often show deficiency of intrinsic factor as an isolated defect, unaccompanied by gastric atrophy or by loss of acid or peptic secretion. It is difficult to provide a unifying hypothesis to account for the differences in gastric physiology in the juvenile and adult forms of the disease, and it is tempting to consider whether they may be totally different in their pathogenesis. Mollin,

Baker, and Doniach's case, however, suggests the necessity for one explanation, since the father of their patient developed classical pernicious anaemia (with gastric atrophy proved by biopsy) in middle age. A unifying hypothesis can be derived from a more detailed comparison of the two forms of the disease. A significant point emerging from recent work on pernicious anaemia is that the failure of gastric function in the classical form of the disease is variable, and not necessarily of great severity. The important biopsy studies of Joske, Finckh, and Wood (1955) showed the variations in gastric histology in patients with proved pernicious anaemia. Only 40 of their 100 patients had complete gastric atrophy of the type usually associated with this diagnosis. The others had changes varying in severity from superficial gastritis with some degree of atrophy to severe atrophic changes short of complete atrophy. Similar evidence is provided by the work of Jacobs (1958), who has shown that some degree of acid secretion by the stomach is common in pernicious anaemia, and that there is no regular relationship between the level of acid secretion and the duration of the anaemia. It is clear that the apparent homogeneity of the biochemical and pathological features of classical pernicious anaemia is to some extent an artifact derived from the crudity of our ordinary methods of assessing gastric function, and that the differences in gastric function between the juvenile and the classical forms of the disease may be differences of degree only.

Any general hypothesis of the pathogenesis of pernicious anaemia must take account of the following findings:

1. The sequence of progressive loss of gastric secretory function, proceeding to complete loss of intrinsic factor and sometimes to pernicious anaemia.

2. The same sequence in people both with and without a family history of pernicious anaemia.

3. Relatives of patients with pernicious anaemia have, on the whole, a lesser capacity to absorb vitamin B_{12} than controls, and therefore presumably a tendency to deficient production of intrinsic factor. This tendency is found in relatives with free gastric acid, as well as in those with achlorhydria (McIntyre, Hahn, Conley, and Glass, 1959).

4. Children suffering from pernicious anaemia may have, despite their gross deficiency of intrinsic-factor production, normal or nearly normal gastric function as judged by histology and by production of acid and pepsin.

5. The family histories of children with pernicious anaemia are much more powerfully suggestive of a genetic factor than are the family histories in classical pernicious anaemia.

6. Juvenile pernicious anaemia and the classical form of the disease have been described in different members of the same family.

These partly discrepant features can be resolved if it is supposed that (*a*) the children with pernicious anaemia provide the examples of homozygous inheritance of the factor responsible for intrinsic-factor deficiency, and that (*b*) a partial deficiency of intrinsic-factor production itself predisposes to atrophy of

the stomach. The possibility that intrinsic-factor deficiency may be the primary defect in pernicious anaemia, and may predispose to gastric atrophy, has been argued strongly on pathological grounds by Magnus (1958). He considered that the various pathological changes are different stages of the same process, and that the evidence points to the view that these changes are a consequence of intrinsic-factor deficiency rather than its cause; the variations in gastric histology and in acid production in pernicious anaemia already discussed, and the erratic incidence of pernicious anaemia in patients with gastric atrophy, do not suggest that loss of intrinsic factor is a simple consequence of gastric atrophy. This view of the pathogenesis of pernicious anaemia also gains support from the results of familial studies. It is clear that what is inherited is a tendency to deficient production of intrinsic factor, a tendency which may or may not be converted into disease. The factors converting the inherited tendency into the disease are probably multiple but, if the inherited tendency itself predisposes to gastric atrophy, a vicious circle can be envisaged: inherited intrinsic-factor deficiency → atrophic gastritis → more severe intrinsic-factor deficiency, culminating in pernicious anaemia. This idea is supported by the finding that the families of patients with pernicious anaemia show a regression of vitamin-B_{12} absorption with age, which is not found in normal controls (McIntyre, Hahn, Conley, and Glass, 1959).

In other patients with pernicious anaemia an acquired gastric atrophy, unrelated to genetic factors, may perhaps be superimposed on the inherited tendency to deficient intrinsic-factor production. Since, however, gastric atrophy has often been shown to precede malabsorption of vitamin B_{12}, at least malabsorption of a severe degree, and since evidence of deficient production of intrinsic factor is not obtained in the families of all patients with pernicious anaemia, the view must be accepted that the disease may sometimes result from acquired gastric disease without a genetic basis. If the exact causes of such unknown acquired gastric atrophy were elucidated, such cases might in the future be excluded from the definition of pernicious anaemia, and grouped rather with megaloblastic anaemias, such as those caused by total gastrectomy and nitric acid burns of the stomach. The possible modes of development of pernicious anaemia are illustrated diagrammatically in Fig. 5.

No direct evidence that the children here reported are homozygous for a heritable factor could be obtained from a study of their parents. Both were healthy, with normal blood counts, uropepsin in the urine, and free acid in the gastric juice, and showed absorption of vitamin B_{12} within the normal range. It is, however, often difficult to detect heterozygous carriers of disease, and McIntyre, Hahn, Conley, and Glass's finding that there is a regression of vitamin-B_{12} absorption with age in relatives of patients with pernicious anaemia indicates that the parents may yet show, later in life, a deficiency of intrinsic factor. It is hoped to keep in touch with both the children and their parents.

Vitamin-B_{12} deficiency and intestinal malabsorption. When first admitted, R. W. showed all the clinical features of coeliac disease. This syndrome may

have resulted from a combination of anaemia and repeated infections, but the question arises whether vitamin-B_{12} deficiency itself could in some way result in intestinal malabsorption. A few observations lend this idea some support. In Benjamin's (1948) patient the diagnosis of pernicious anaemia was established by showing that another patient with known pernicious anaemia exhibited

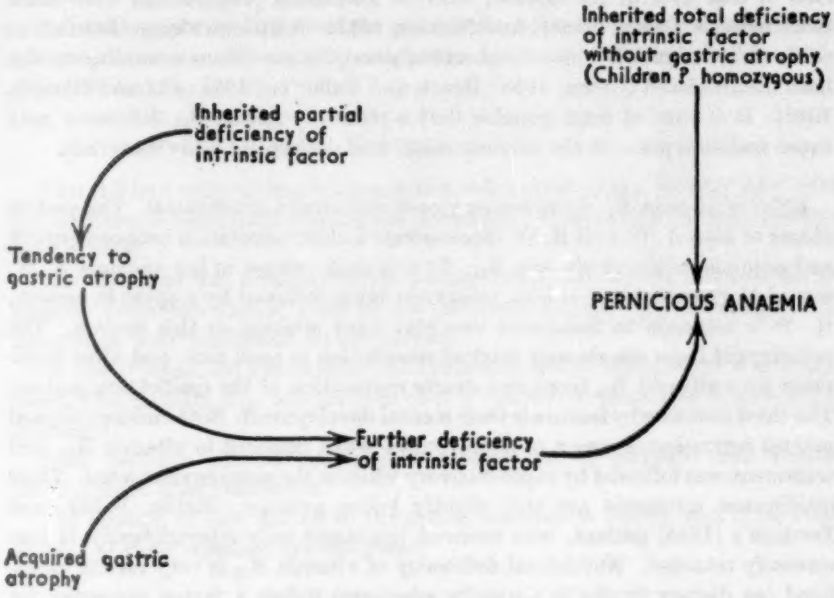

FIG. 5. Possible modes of development of pernicious anaemia.

a reticulocytosis after receiving subeffective amounts of liver digested with normal gastric juice, but not after receiving liver digested with the patient's gastric juice. Benjamin also made a test of this sort on the patient herself during a relapse, and found no reticulocytosis either after the administration of liver digested with normal gastric juice or after liver digested with the patient's own juice. This suggests that during relapse there was a temporary failure of absorption of anti-pernicious-anaemia principle, despite a fat absorption of 96 per cent., a normal glucose tolerance, and normal X-rays of the gastrointestinal tract. This suggestion was supported by the observation that, during a severe relapse, the patient showed no response to large amounts of a liver and stomach preparation given orally, but a prompt response to liver injections. A further suggestion, that vitamin-B_{12} deficiency may in some circumstances actually cause poor intestinal absorption of the vitamin, is provided by the work of Mollin, Booth, and Baker (1957). In a study of vitamin-B_{12} absorption in a group of patients suffering from malabsorption syndromes with megaloblastic anaemia, six patients were tested again after treatment of their

anaemia with vitamin B_{12} or folic acid. Two of these patients now showed an improved absorption of vitamin B_{12}.

Finally, it is of great interest that Castle, in the series of papers in which he established the pathogenesis of pernicious anaemia, suspected that absorption of the product of interaction of intrinsic factor and extrinsic factor was impaired in some cases of pernicious anaemia. He noticed a wide variability in effectiveness of oral liver in the disease, whereas parenteral preparations were much more reliable (Castle, Heath, and Strauss, 1931). A little evidence that factors other than vitamin B_{12} may be absorbed poorly in pernicious anaemia has also been accumulated (Groen, 1938; Heath and Fullerton, 1935; Erf and Rhoads, 1940). It is thus at least possible that a state of vitamin-B_{12} deficiency may cause malabsorption of the vitamin itself, and perhaps of other materials.

Effect of vitamin-B_{12} deficiency on growth and mental development. The growth charts of both A. W. and R. W. demonstrate a close association between growth and administration of vitamin B_{12}. During each relapse of her anaemia A. W. ceased to grow and lost weight, treatment being followed by a spurt in growth. R. W.'s response to treatment was also most striking in this respect. The radiological bone age showed marked retardation in each case, and after treatment with vitamin B_{12} there was steady maturation of the ossification centres. The third noteworthy feature is their mental development. Both children showed mental regression or arrest of development when deficient in vitamin B_{12}, and treatment was followed by rapid recovery while in the same environment. Their intelligence quotients are still slightly below average. Mollin, Baker, and Doniach's (1955) patient, who received treatment only intermittently, is also mentally retarded. Nutritional deficiency of vitamin B_{12} is very rare in childhood (as dietary intake is normally adequate) unless a factor necessary for absorption or utilization of the vitamin is absent, and it is therefore rarely possible to assess the effect of this deficiency on growth. Cessation or disturbance of growth has, however, been found in several of the reported children with pernicious anaemia (Stevenson, Little, and Langley, 1956; Benjamin, 1948; Mollin, Baker, and Doniach, 1955); Stevenson, Little, and Langley's and Benjamin's patients showed striking acceleration of growth on treatment. The relationship of vitamin B_{12} to growth in rats, pigs, and other species is well documented (Peterson and Register, 1958; Luecke, McMillen, Thorp, and Boniece, 1949; Nichol, Dietrich, Cravens, and Elvehjem, 1949). A variety of important metabolic effects of vitamin B_{12} which might account for this have been described, including a relationship between vitamin B_{12} and thyroid function in chicks (Ferguson, Trunnell, Dennis, Wade, and Couch, 1957; Ferguson, Rigdon, and Couch, 1957). The effect of vitamin B_{12} as a stimulant of appetite and growth in normal children has not been so definite. A significant increase in growth has been demonstrated by Crump and Tuly (1955) in selected children of poor physique, and by other workers (Wetzel, Fargo, Smith, and Helikson, 1949; Chow, 1952; Larcomb, Perry, and Peterman, 1954; Wilde, 1952). The majority of studies, however, show no conclusive evidence that vitamin B_{12}

stimulates growth or appetite in normal children (Report of Committee on Nutrition, 1958).

We are grateful to Dr. B. E. Schlesinger and Dr. S. Yudkin for permission to study these cases, to Dr. M. Shiner for the biopsies, and to Dr. Mollin for the vitamin-B_{12} assays.

Since this paper was accepted for publication a further report of two siblings suffering from juvenile pernicious anaemia has been published: Leikin, S. L. (1960) *Pediatrics*, **25**, 91.

Summary

Two children with pernicious anaemia are described in one family; they were the offspring of the second marriage of one parent. Children by the first marriage were normal.

The diagnosis was established by demonstrating absence of intrinsic-factor activity from the gastric juice of the patients. Studies of ^{58}Co-vitamin-B_{12} absorption were performed on the parents.

One child presented a malabsorption syndrome, which disappeared after treatment with vitamin B_{12}, and the role of this vitamin in intestinal absorption is discussed.

Both patients showed remarkable acceleration of physical and mental development after treatment.

The relation of this disease to pernicious anaemia in adults, and the pathogenesis of these diseases, are discussed.

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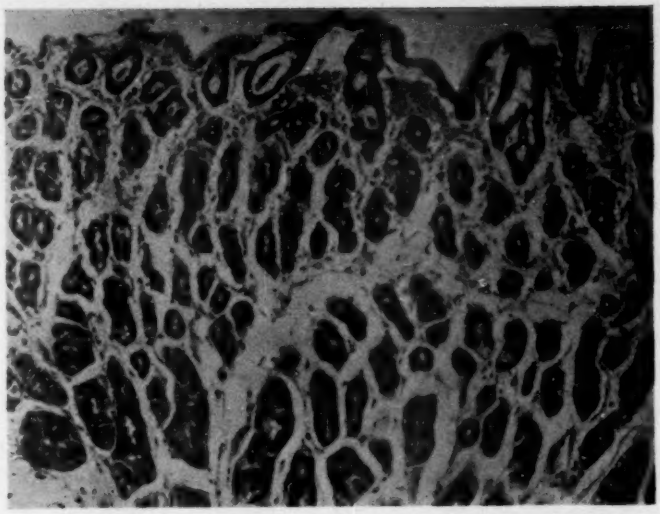

FIG. 6. Photomicrograph of section of stomach from A. W.

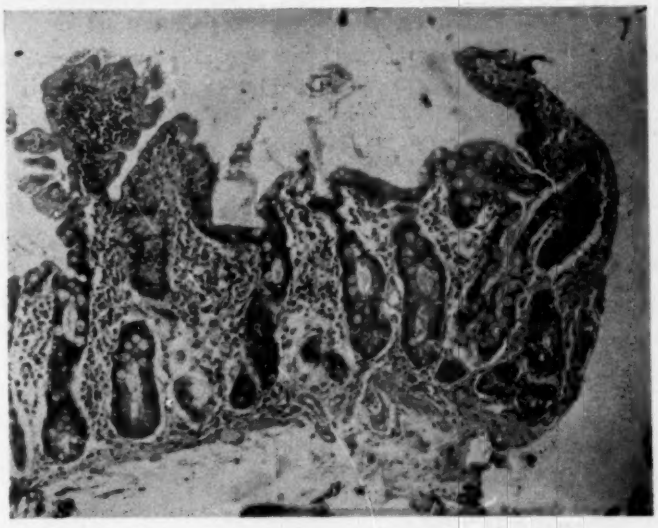

FIG. 7. Photomicrograph of section of duodenum from A. W.

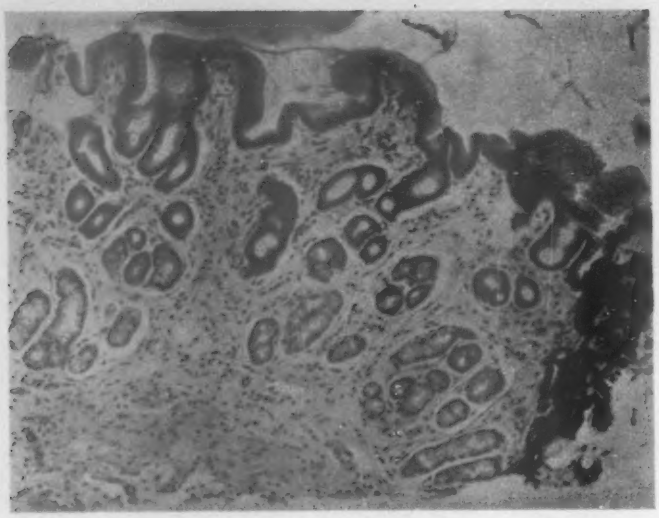

FIG. 8. Photomicrograph of section of stomach from R. W.

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CONGENITAL HEPATIC FIBROSIS[1]

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With Plates 14 and 15

Portal hypertension may result from extrahepatic venous obstruction, distortion of the intrahepatic vasculature, or obstruction of the hepatic veins. In Great Britain the syndrome is uncommon, if not rare, in childhood, and almost always results from extrahepatic obstruction or intrahepatic disease. The distinction between these two main groups of cases is important in view of the difference in prognosis and treatment; it is usually possible to distinguish them on clinical grounds alone, and a definite answer can almost always be given with the aid of needle biopsy of the liver and portal venography. A more difficult problem is the classification of the children with intrahepatic obstruction. These cases were formerly grouped together as 'juvenile cirrhosis'. During the nineteenth century the only generally recognized cause of cirrhosis was alcohol; the occurrence of a similar lesion in a child, therefore, gave rise to considerable comment and a searching inquiry into the child's alcoholic consumption, which made the early case reports very quaint reading (Osborn, 1881). More recently it has been suggested that a pathological picture, basically similar to that of Laennec's cirrhosis in the adult, can be produced in children by neonatal hepatitis (Stokes, Wolman, Blanchard, and Farquhar, 1951; Bodian and Newns, 1953; Dible, Hunt, Pugh, Steingold, and Wood, 1954; Honé, 1954; Sherlock, 1955), blood-group incompatibility (Ehrlich and Ratner, 1955), Fanconi's syndrome (Baber, 1956), and Wilson's disease. It may occur in families carrying the necessary gene for Wilson's disease, even in the absence of other features of the disease (Chalmers, Iber, and Uzman, 1957; Lygren, 1959). It is probable that other, as yet unrecognized, genetic defects account for some of the cases of 'juvenile cirrhosis of unknown aetiology'. The raised portal pressure in these patients is associated with severe distortion of the fine architecture of the liver.

More rarely portal hypertension results from lesions in the liver distinct from Laennec's cirrhosis, in which the fine architecture is better preserved. The liver lesion associated with fibrocystic disease of the pancreas (Andersen, 1938; Pugsley and Spence, 1949; Bodian, 1952; Webster and Williams, 1953; di Sant'

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Agnese, 1956; di Sant' Agnese and Blanc, 1956; Gibson and Rodgers, 1957) is probably of this type; though some of the cases described have closely resembled Laennec's cirrhosis, others have had reasonable preservation of lobular architecture. Only about one patient in 12 with hepatic involvement develops portal hypertension (di Sant' Agnese and Blanc, 1956) though this small incidence may be due to the short survival of many such patients. The incidence of portal hypertension in patients with congenital cystic liver, in which fine architecture is usually well preserved, is even lower: Melnick (1955) found no evidence of it in 70 cases, many of long survival.

A fibrotic change in the liver distinct from cirrhosis, and not associated with disease of the pancreas, was described 31 years ago (MacMahon, 1929). The distinguishing features are the maturity of the fibrous tissue, the relatively normal architecture in the areas unaffected by fibrosis, and the presence of striking abnormalities of the interlobular bile-ducts. The coexistence of this lesion with congenital cystic disease of the kidneys has suggested that it is a variant of congenital cystic liver. It differs from the latter condition in that large cysts are absent and portal hypertension is often present. Until recently this condition has been regarded as a pathological curiosity, and has been recognized only at autopsy. Most of the descriptions contain only scant reports of the clinical features. Parker (1956) described six patients who showed this lesion *post mortem* under the title 'Fibrosis of the liver as a congenital anomaly'. We have paraphrased his title to provide a name for the disease, 'congenital hepatic fibrosis'. We here describe 13 patients with congenital hepatic fibrosis who have been seen by us on account of bleeding oesophageal varices or hepatosplenomegaly, with a review of the cases previously reported. It is suggested that this disease accounts for a significant proportion of the cases of portal hypertension in children and young adults, and that the clinical course differs from that of cirrhosis.

Patient 1 is a girl born on 29.6.55 after a normal pregnancy and normal full-term delivery. The mother has been healthy, and never jaundiced except in her own neonatal period; the father suffers from asthma, is otherwise healthy, and has never been jaundiced; there is no consanguinity between the parents. There are no siblings.

The child developed normally until the age of 16 months, when abdominal distension was noticed during convalescence from measles. Since then abdominal protuberance has been progressively obvious, and her growth has lagged, her height and weight being below the 10 percentile for her age. Mental development has progressed normally. At 18 months she was seen at the North Middlesex Hospital, where gross enlargement of the liver and spleen was found. Investigation revealed normal liver function apart from a high alkaline phosphatase level (Table II), a leucocytosis and slight anaemia (Table III), erythrocyte sedimentation rate of 35 mm. in one hour, negative Paul–Bunnell, Wassermann, and Kahn reactions, normal blood-sugar, and no sugar, albumin, or abnormal cells in the urine. Chest X-rays showed a fine miliary mottling, which has remained unchanged on three subsequent films over 18 months, and is thought to be due to pulmonary microlithiasis. No similar lesion is present on the chest films of the parents. The patient's blood group

was A Rh +; the mother's group was also A Rh +, and no antibodies were detected in her serum.

Diagnostic laparotomy was carried out, and confirmed the enlargement and firmness of the liver and spleen. Operative biopsy of the liver was done, from which the diagnosis was established. The patient has been followed up at Hammersmith Hospital and, although she has so far escaped gastrointestinal haemorrhage, her progress is disappointing. The lag in growth is increasing, and she is rather listless and eats poorly.

Patient 2 is a girl born on 13.2.51 after a normal pregnancy and normal full-term delivery. Her parents are healthy and have never had jaundice, and there is no consanguinity. She has one sister a year older than herself, who is entirely healthy and has no palpable enlargement of the liver or spleen.

The patient developed normally until the age of five years. She then suffered from recurrent sore throats and otitis media, and was admitted to the Royal Buckinghamshire Hospital for tonsillectomy at the age of six. Pre-operative examination revealed hepatosplenomegaly, and the tonsillectomy was therefore cancelled; she has since outgrown her upper respiratory symptoms without operation. She was transferred to Hammersmith Hospital for investigation. There was no history of jaundice or dark urine, but the parents had noted pale stools on a number of occasions. A hard, somewhat irregular liver was palpable three finger-breadths below the right costal margin, and a firm spleen a similar distance below the left. There was a single dilated superficial vein over the upper abdomen. At no time did the patient show mental changes, tremor, fetor, or any of the cutaneous manifestations of liver disease.

Investigation revealed normal liver function (Table II), slight anaemia, a normal white-cell count (Table III), erythrocyte sedimentation 6 mm. in one hour, no albumin, sugar, bile, or excess of urobilinogen in the urine, and normal chest X-rays. Portal hypertension was confirmed by a barium swallow, intrasplenic pressure measurement, and a splenic venogram (Table IV). A duodenal ulcer was also demonstrated. The diagnosis of congenital hepatic fibrosis was established by needle biopsy of the liver under general anaesthesia.

The patient has since remained very well, growing at about the same rate as her elder sister, and with no evidence of gastrointestinal bleeding. She has had occasional slight frequency of micturition; a catheter specimen of urine in August 1957 showed scanty pus and red cells, and yielded a scant growth of *Streptococcus faecalis* and *Proteus vulgaris*. An intravenous pyelogram was done in May 1958, and showed rather large kidneys, with foetal lobulation of the left. The inferior calyx was stretched on the left side, suggesting a diagnosis of polycystic kidney.

Patient 3 is a girl born on 6.12.49 after a normal pregnancy and normal full-term delivery. Her parents are healthy; they have never been jaundiced, and there is no consanguinity. She has four siblings aged three to 12 years, all of whom are healthy, have no stigmata of hepatic or renal disease, and have never been jaundiced. The two elder siblings have given normal results to liver-function tests.

The patient remained well, apart from occasional bronchitis, until the age of five years, when she was admitted to Whipps Cross Hospital after passing a melaena stool. Over the following two years she had four further melaena stools, and on two occasions admission to hospital was followed by a haematemesis. Blood transfusion was required on three occasions. Between episodes of bleeding she appeared perfectly well, but for a day or two after each episode she seemed 'dopey'.

At the age of seven she was referred to Hammersmith Hospital; she was a pale child, of normal height and weight for her age, and well developed mentally. Several spider naevi and slight palmar erythema were present. The liver was firm but not enlarged; the spleen was palpable 2 cm. below the left costal margin, and was firm. The urine contained no albumin, sugar, bile, or microscopic abnormality. Liver-function tests (Table II) and blood counts (Table III) gave normal results. An electroencephalogram was normal, and was not affected by high-protein diet. Portal hypertension and a large collateral circulation were demonstrated by intrasplenic-pressure measurement, barium swallow, and cine-trans-splenic venogram. A barium meal also showed a duodenal ulcer. End-to-side portacaval anastomosis was performed on 13.11.56. The liver was firm and slightly enlarged, but otherwise appeared normal. A surgical biopsy specimen was taken, from which the diagnosis was subsequently established.

The post-operative course was marked by prolonged pyrexia and chest infection. A post-operative cine-trans-splenic venogram showed occlusion of the portacaval anastomosis, and large collateral channels via the splenic and left gastric, parasplenic, and mesenteric vessels. Gastrointestinal haemorrhage recurred two months after the operation, and necessitated re-exploration on 14.3.57, when splenectomy and a modified Talma–Morrison procedure were carried out. The spleen weighed 180 g., and showed the typical appearance of congestive splenomegaly. Hilar lymph-nodes showed sinus hyperplasia, and iron pigment in reticulo-endothelial cells.

There has been one further episode of haematemesis and melaena in June 1957, not requiring transfusion, and the patient has otherwise been well apart from rather frequent colds. She now lags behind her siblings in growth, but not in mental development. Her height and weight in June 1958 were below the 10 percentile for her age. Her urine has contained a trace of albumin on a number of occasions, and hyaline and granular casts are also now present. The blood-urea remains normal. An intravenous pyelogram in January 1957 showed no abnormality except depression of the left kidney by the spleen.

Patient 4, a boy born on 3.10.49, was healthy until the age of six years, when he was seen on account of haematemesis and melaena which required transfusion. A firm liver was palpable 2 cm. below the right costal margin, and a firm spleen 1 cm. below the left. A salmonella was isolated on blood culture, and subsequently from the faeces and the gall-bladder. It proved resistant to all available antibiotics. During the next 12 months the patient had repeated haematemeses, often requiring transfusion, and was in hospital almost continuously. He was transferred to Bristol Royal Infirmary for surgery on 13.6.57.

Pre-operative liver-function tests gave normal results (Table II), but the haemoglobin was slightly reduced (Table III). A pre-operative trans-splenic portal venogram showed a large shunt through the left gastric vein, and no filling of the portal vein (Plate 15, Fig. 7). An operative venogram via a jejunal vein showed some filling of the portal vein, and a retrograde shunt via the splenic vein into the left gastric vein (Plate 15, Fig. 8). Portal hypertension was confirmed by direct measurement (Table IV). End-to-side portacaval anastomosis was performed on 24.6.57. The liver was firm, smooth, and mottled; a surgical biopsy specimen was taken. A large collateral vessel was present in the falciform ligament. The portal vein was of normal size, and was surrounded by numerous large lymph-nodes. There has been no complaint of renal symptoms, and the urine contained no albumin or sugar. The right kidney was seen at operation, and no abnormality was noted. Since the operation the patient has suffered from recurrent bouts of fever, attributed to exacerbations of his

salmonella infection; positive cultures have been obtained from the faeces until his most recent admission in September 1959. His general health is now poor.

Patient 5, a girl born on 20.10.46, developed normally until the age of five years, when she was seen on account of haematemesis and melaena. The liver was enlarged and firm, and a firm spleen was palpable 2 cm. below the left costal margin. Liver-function tests gave a normal result (Table II). A barium swallow was normal, but oesophagoscopy revealed extensive varices. The presence of a collateral circulation was also demonstrated by trans-splenic portal venography (Table IV). She was readmitted during a second haematemesis at the age of seven, and emergency surgery was undertaken. The liver was firm, and showed a fine fibrosis; a biopsy specimen was taken. Portal hypertension was confirmed by direct measurement (Table IV). The portal vein was large and thin-walled, and there were prominent collateral veins in the falciform ligament and on the deep surface of the anterior abdominal wall. An end-to-side portacaval anastomosis was performed. The post-operative course was smooth, and within six months the spleen had receded behind the costal margin. The patient remains well, leading a normal life. Neither liver nor spleen is now palpable, and the results of liver-function tests have remained consistently normal. There has been no complaint of urinary symptoms; the urine contained no albumin or sugar before operation. An intravenous pyelogram in 1954 showed a normal right kidney, and slight distortion of the calyces on the left, changes insufficient to justify a diagnosis of congenital cystic kidneys.

Patient 6 is a girl born on 29.3.45 of healthy parents with no history of jaundice and no consanguinity. She had one elder sister, aged 28, who has not been personally examined but is alive and well, without any history of disease of the liver or kidneys. Two other siblings died, one being still-born and the other dying of pneumonia at three months; there was no autopsy in either case. The mother was aged 39 at the time of the patient's birth, but pregnancy, delivery, and infancy were normal. At the age of two years the child was admitted to Doddington Hospital for repair of an umbilical hernia. Hepatomegaly was noted, and she was found to have albumin, pus cells, and casts in the urine. There was no haematuria. The urinary findings cleared up in a few days, and were attributed to a subclinical attack of acute glomerulonephritis. At the age of three she had a brisk haematemesis, and there were five further haematemeses between the ages of nine and 12. She remained pale, and at the age of 11 was treated for iron-deficiency anaemia. There was a transient attack of dysuria at the age of five, and pneumonia at the age of seven.

When 12 years old she was referred to Hammersmith Hospital with a diagnosis of portal hypertension. She was a tall, thin, pale, intelligent girl, with no cutaneous manifestations of liver disease. Height, weight, and sexual development were within the normal limits for her age. The liver was hard, and the left lobe enlarged and irregular; the spleen was firm, and extended 2 cm. below the left costal margin; a few dilated superficial veins, with upward flow, crossed the costal margins. The urine contained no sugar, albumin, bile, excess of urobilinogen, or microscopic abnormality. Liver-function tests (Table II) and blood counts (Table III) gave normal results. An intravenous pyelogram was normal. Portal hypertension was confirmed by intrasplenic pressure measurement (Table IV), and the presence of a collateral circulation was demonstrated by barium swallow and trans-splenic portal venography (Table IV). The diagnosis of congenital hepatic fibrosis was made tentatively from a needle biopsy of the liver, and was subsequently confirmed by a surgical biopsy.

End-to-side portacaval anastomosis was performed on 6.3.58 at Bristol Royal Infirmary. A normal-sized right hepatic lobe and a very tough, smooth, enlarged left lobe, with a scalloped free margin, were found. The right kidney appeared normal. The portal vein was of normal size; the raised portal pressure was confirmed (Table IV). The post-operative course was smooth, and the patient remains well.

Patient 7, a girl born on 9.3.35, was well until the age of 16, when she was seen at St. Austell Hospital with iron-deficiency anaemia, and a transfusion of two pints of blood was given. Enlargement of the liver and spleen was noted, and at laparotomy the liver was found to be 'much enlarged and cirrhotic'. She had a haematemesis at the age of 17, and three further episodes requiring transfusion at the age of 20. She was transferred to Bristol Royal Infirmary with a diagnosis of portal hypertension. The liver was hard and enlarged, and the spleen was palpable 3 cm. below the costal margin. Liver-function tests gave normal results (Table II). Portal hypertension was confirmed at operation by direct measurement (Table IV). End-to-side portacaval anastomosis was performed on 14.1.57; a large, hard liver was found, with some irregular nodules, and many vascular adhesions on the surface. No abnormality of the right kidney was noted at operation. The portal vein was of normal size. Since her operation the patient has progressed well, and is in training as a nurse.

Patient 8 was a girl born on 7.1.54 after a normal pregnancy and delivery. Her parents were healthy and had never been jaundiced, and there was no consanguinity. She developed normally until the age of two and a half years, when her mother noticed a firm swelling in the right hypochondrium, causing protuberance of the abdomen. She was admitted to the Royal Hospital for Sick Children, Glasgow, where laparotomy was carried out. Pre-operative blood counts were normal (Table III). The enlargement of the liver involved the left lobe predominantly, and the surface was nodular. A surgical biopsy specimen was taken. After the operation she became jaundiced, with bile and excess of urobilinogen in the urine; the episode cleared up within four days. Post-operative liver-function tests (Table II) showed an increase in serum alpha-2 and beta globulins, and a moderate rise in the level of serum alkaline phosphatase. Cystic fibrosis of the pancreas was excluded by analysis of sweat, which had an electrolyte content of sodium 40, potassium 15, and chloride 49 m–equiv. per litre. A month later the patient was again jaundiced for three weeks, and thereafter she had slight intermittent jaundice associated with scratching. At the age of three she had gross enlargement of the liver, a firm spleen palpable 2 cm. below the left costal margin, and some dilated superficial veins over the upper abdomen.

At this time she was seen in Hammersmith Hospital. Portal hypertension was demonstrated by intrasplenic pressure measurement, but no collateral circulation was shown on the trans-splenic portal venogram or barium swallow (Table IV). Liver-function tests showed a further increase in serum alkaline phosphatase to 57 King–Armstrong units per 100 ml., and an increase in serum alpha-2 and beta globulins. Needle biopsy of the liver was again suggestive, but not diagnostic, of congenital hepatic fibrosis. Jaundice subsided, but recurred a year later, and the patient then developed gross ascites and marked dilatation of veins on the abdominal wall. She became listless, but no other features of hepatic pre-coma were noted. The stools became loose, and increased in frequency up to 10 per day. The ascites responded for a while to chlorothiazide therapy, but after a month paracentesis became necessary. Seven litres of

fluid were removed, but the ascites reaccumulated rapidly, and the patient died suddenly during the course of a second paracentesis.

Findings at autopsy. No oesophageal varices were seen, and no abnormality noted in the portal vein. The liver weighed 720 g.; there was a deep, irregular scar in the middle of the right lobe, and the left lobe was small and irregular; the whole surface was finely nodular. A large bile-filled cavity occupied a quarter of the left lobe. The cyst had an epithelial lining, and opened into a bile-duct that could be traced to the hilum of the liver but did not connect with the common bile-duct. There was some distension of the bile-duct system towards the hilum of the right lobe. The gall-bladder and extrahepatic ducts were normal. The spleen weighed 220 g., and was firm. The lymphoid tissue was visible on the cut surface. Histologically it showed fibrosis, dilated sinusoids, and areas of haemorrhage. The kidneys, pancreas, adrenals, pituitary, brain, and heart showed no abnormality except bile staining. The lungs showed only acute bronchitis.

Patients 9, 10, and 11 are the three siblings of one family. They were brought to our notice by Mr. G. Wooler, who carried out the portacaval anastomoses on patients 9 and 10 at Leeds General Infirmary. The parents are healthy; the father has not been examined personally, but the mother on examination has no stigmata of liver disease. Neither parent has ever been jaundiced. There is no known consanguinity, but both parents come from the same locality in rural Yorkshire. The children were originally investigated at Huddersfield Royal Infirmary by Dr. W. P. Sweetnam, who reported the elder girl and boy (Sweetnam, 1955). Congenital hepatic fibrosis was not then recognized as an entity, and they were thought to be suffering from an unusual familial form of cirrhosis. In view of the interest then current in blood-group incompatibility as a cause of congenital cirrhosis, the genotypes of the family were investigated by Dr. Parkin at the Blood Group Reference Laboratory of the Lister Institute of Preventive Medicine, with the following results:

Subject	*ABO*	*Rh phenotype*	*Probable genotype*	*MN*	*S*	*P*	*Lu*	*K*	*Le^a*	*Le^b*	*Fy^a*
Father	B	CCDee	CDe/CDe	MN	+	+	—	—	..	..	+
Mother	O	ccDEe	cDE/cde	N	—	+++	—	—	+	—	+
Patient 9	O	CcDee	CDE/cde	N	—	—	—	—	—	+	+
Patient 10	B	CcDee	CDe/cde	N	—	+++	—	—	..	..	+

The mother's serum was tested against a comprehensive panel of cells covering the Rh, MNSs, P, Lu, Kell, Lewis, Duffy, and Kidd orders of inheritable blood-groups. The tests were done against cells in saline and albumin at 37° C, 20° C, and 4° C, and by the indirect anti-human-globulin technique, using several batches of Coombs reagent. No abnormal antibody was demonstrated.

Patient 9, a girl born on 24.5.48 after a normal pregnancy and normal full-term delivery, was operated upon for umbilical hernia at two years of age, and no other abnormality was recorded at that time. In October 1953, at the age of five, she had a brisk haematemesis requiring a two-pint transfusion. A hard, enlarged liver was found, and the spleen was palpable. Liver-function tests gave normal results (Table II). Blood counts revealed a mild normochromic

anaemia and thrombocytopenia (Table III). A catheter specimen of urine contained no albumin or sugar, and was normal on microscopy; the blood urea was 30 mg. per 100 ml. Portal hypertension was confirmed by hepatic vein catheterization, and collateral circulation was demonstrated by barium swallow, trans-splenic portal venography, and oesophagoscopy (Table IV). Side-to-side portacaval anastomosis was performed on 25.2.54. The liver was enlarged, and appeared cirrhotic. The gall-bladder was greatly distended, but there was no obvious disease in it or in the major bile-ducts. Portal venous pressure was elevated to 30 mm. Hg. There was much lymphatic tissue adhering to the portal vein. On histological examination this tissue contained moderate fibrosis and numerous eosinophils. The circulating eosinophil count at the time was 1,100 per cu. mm. Since operation the patient has grown normally, but has been rather backward at school. She has had bronchopneumonia following measles, and a period of iron-deficiency anaemia between 1954 and 1959.

She was again investigated at Hammersmith Hospital in 1959. Normal physical development was found, with slight mental retardation (relative age nine years on the Schonell word list; intelligence quotient 77 per cent. on the Wechsler scale for children). There were numerous spider naevi, well-marked fetor hepaticus, a large, hard liver, and the spleen was just palpable. There was no 'flapping' tremor, and the electroencephalogram showed only a minimal slowing of the dominant frequency. The arterial blood ammonia level was 1·3 μg. per ml. on a normal diet. A course of low-protein diet and paromomycin, to sterilize the gut, produced no alteration in the arterial ammonia, electroencephalogram, or mental performance. The urine contained no albumin, sugar, bile, excess of urobilinogen, or microscopic abnormality. Urine could be concentrated to a specific gravity of 1,025. A needle biopsy of the liver established the diagnosis of congenital hepatic fibrosis; the liver felt extremely hard.

Patient 10, a boy born on 31.10.49 after a normal pregnancy and normal full-term delivery, developed normally until the age of two years and six months, when he was seen at Huddersfield Royal Infirmary on account of anorexia, pallor, and abdominal swelling. His weight (28 lb.) was normal for his age and sex. The liver was palpable 4 cm. below the costal margin. Liver-function tests (Table II) gave normal results; the urine contained no albumin, sugar, or microscopic abnormality; the blood urea was 25 mg. per 100 ml., and an intravenous pyelogram was normal. Diagnostic laparotomy on 27.5.52 revealed a large liver, which appeared cirrhotic, and a slightly enlarged spleen. A biopsy specimen of the liver was taken.

In August 1952 he had a small rectal haemorrhage, probably from haemorrhoids, and his stools contained occult blood. Abdominal swelling increased, and superficial abdominal veins became prominent. Liver-function tests again gave normal results in September 1953. In May 1954 (aged four years seven months) he had a haematemesis requiring transfusion. The spleen was now palpable 2 cm. below the costal margin. An extensive collateral circulation, including the haemorrhoids, was demonstrated by portal venography (Plate 15, Fig. 6), and oesophageal varices were also shown on barium swallow and oesophagoscopy (Table IV). Side-to-side portacaval anastomosis was performed on 9.9.54. Portal hypertension was confirmed by direct measurement (Table IV). Success of the operation was confirmed by shrinkage in the size of the spleen, disappearance of occult blood from the stools, and a trans-splenic portal venogram which showed the whole of the contrast medium in the portal vein by-passing the liver into the inferior vena cava. His physical development has been normal since operation, but there has been some mental retardation, partly

due to emotional upset. Numerous spider naevi appeared on the face in 1956, and he has since had occasional epistaxis, though no spider naevi are visible in the nose.

When seen at Hammersmith Hospital in April 1959, aged nine years, he was shy and backward, with an intelligence quotient of 85 per cent. on the Weschler scale and a relative age of six years on the Schonell word list. There was gross hepatic fetor, slight 'flapping' tremor, minimal slowing of the electroencephalogram, and an arterial blood ammonia level of 1·4 μg. per ml. A two-week course of protein restriction and oral paromomycin caused no change in arterial ammonia, but there was slight improvement in the electroencephalogram and in performance on intelligence testing. He has since been maintained on a 40 g. protein diet and neomycin. The 4-cm. enlargement of the liver was still present, and involved the left lobe disproportionately. The spleen had regressed to the left costal margin. Liver function was normal except for an alkaline phosphatase level of 21 King–Armstrong units. There was a slight normochromic anaemia (12·6 g. haemoglobin per 100 ml.), and a leucocytosis of 11,000 per cu. mm. The blood urea was 40 mg. per 100 ml., and serum electrolytes normal. The urine contained a gross increase of all amino acids, but was otherwise normal. Intravenous pyelography showed changes typical of congenital cystic kidneys. The diagnosis of congenital hepatic fibrosis was confirmed by needle biopsy of the liver. The histological appearances were similar to those found in the original surgical biopsy. The liver was so hard that it bent the biopsy needle. The patient remains well, though somewhat backward at school.

Patient 11, a girl born on 9.1.55 after a normal pregnancy and normal full-term delivery, was followed with particular care in view of her family history. She appeared normal at birth, and it was noted that the liver was of normal size for her age and that the spleen was not palpable. She developed normally during infancy, and it was specifically mentioned that at the age of 11 months her liver had regressed in relative size in a normal manner. She was walking well, and appeared normal for her age, when seen at a routine clinic visit in July 1957 at the age of 30 months. The following month she contracted an upper respiratory infection which spread to the chest and did not respond to antibiotics, and it was then noted that her liver was firm and extended 4 cm. below the right costal margin. She was admitted to the Royal Infirmary, Huddersfield, where further antibiotic therapy was without effect, the child remaining ill, pale, apathetic, and irritable. Liver-function tests gave normal results except for the serum–albumin level, which fell three weeks before her death; at this point she became oedematous, with ascites that reaccumulated rapidly after paracentesis in spite of restriction of dietary sodium. She became drowsy, and was given neomycin therapy, but lapsed into a coma a few hours before death.

Autopsy revealed a pyaemia due to Friedländer's bacillus, with endocarditis on the wall of the left ventricle and abscesses in the left kidney. The gastro-intestinal tract was normal, with no evidence of varices. The liver weighed 1,080 g., and the surface showed 'mild lobulation'. On cut section there was dense fibrosis. No abnormality was noted in the gall-bladder, bile-ducts, or portal vein. The spleen weighed 90 g., and was tough on section. There were numerous enlarged lymph-nodes in various sites, particularly the portal fissure and superior border of the pancreas. No large cysts were present in liver, kidneys, or pancreas, but on histological examination the kidneys showed the typical appearance of the juvenile form of congenital cystic disease.

Patient 12 is a girl born on 7.4.48 after uneventful pregnancy and normal full-term delivery. The parents are healthy and have never been jaundiced, and there is no consanguinity. She has four siblings, aged four to 25, who have never been jaundiced and have no stigmata of liver disease. Three have been personally examined; they have no enlargement of the liver or spleen, and are normal as regards blood counts and liver-function tests. The patient had otitis media with febrile convulsions at the age of two years, but was otherwise normal until January 1956 (aged seven), when her mother noticed abdominal protuberance. In March 1956, at a routine examination, she was found to have a firm spleen extending to the umbilicus. She was admitted to Shrodells Hospital for investigations and later transferred to Hammersmith Hospital. The left lobe of the liver was firm and slightly enlarged, but the right lobe was not palpable. Numerous dilated superficial veins were visible over the abdominal wall. A few petechiae and ecchymoses were present. Her weight was just within the lower 3 percentile for her age and sex, but she was said to be shorter and lighter than her siblings at the same age, and her subsequent growth has similarly lagged behind.

Liver-function tests (Table II) gave normal results, but blood counts showed a pancytopenia, attributed to hypersplenism (Table III). A barium swallow was normal, but collateral circulation was demonstrated by portal venography (Table IV). Liver biopsy, performed on two occasions, produced small fragments of normal hepatic tissue, but the liver felt extremely hard.

She remained well, apart from occasional attacks of left-sided abdominal pain and vomiting, and rather bulky, foul-smelling stools, until November 1958. Between November 1958 and January 1959 she complained of fluctuating pain in the right flank and headache, and pallor was noticed. In January 1959 she had a haematemesis requiring transfusion. Investigations to exclude Wilson's disease (serum copper oxidase, phosphate, and uric acid), pancreatic fibrosis (sweat test), and Fanconi's syndrome (urinary amino acids: high normal level), were all negative. Bone marrow was normal. Side-to-side portacaval anastomosis was performed in February 1959. The liver was firm and irregular; the left lobe was enlarged, and the right lobe of normal size. There was a moderately large choledochous cyst. The portal vein appeared normal. End-to-side anastomosis was performed, the cyst was removed, and the common hepatic duct implanted into the duodenum. Recovery has been uneventful, and the patient is progressing well. Mental development is normal for her age.

Patient 13, a boy born in April 1945, developed normally until the age of nine, when a school medical officer noted abdominal distension, and found enlargement of the spleen to the umbilicus and 2 cm. enlargement of a hard liver. He was investigated at Neath General Hospital and Bristol Royal Infirmary. Oesophageal varices were shown on a barium swallow and a trans-splenic portal venogram (Table IV); the results of liver-function tests, including alkaline phosphatase, were normal (Table II). There was a slight anaemia and leucopenia (Table III). He remained in good health until June 1959 (age 14), when he had haematemesis and melaena, requiring transfusion of seven pints of blood, after which he developed a transient ascites. The bilirubin was now 0·8 mg. per 100 ml., alkaline phosphatase had increased to 33 King–Armstrong units per 100 ml., and leucopenia and thrombocytopenia were more pronounced. A portal venogram showed a long, rather tortuous and irregular portal vein, suggesting intravascular thrombosis.

Laparotomy was carried out on 28.7.59. Many adhesions were found in the porta hepatis. A firm mass of 5 cm. diameter was found in the head of the

pancreas, from which 15 ml. of colourless turbid fluid were aspirated. This fluid had a pH of 7·2, protein content of 0·6 per cent., and no tryptic activity. The gall-bladder and common bile-duct were dilated, and it was thought that this was due to obstruction by the cystic pancreas. Anastomosis of the gall-bladder to the duodenum was performed. Portal hypertension was confirmed (Table IV), but in view of the likelihood of thrombosis in the portal vein it was decided that spleno-renal anastomosis should be undertaken later. After the operation the patient became drowsy, and developed fever, ascites, and jaundice. Liver-function tests showed steady deterioration as jaundice deepened, and he died on 21.9.59.

Autopsy showed extensive thrombosis in the portal, splenic, and mesenteric veins, with incomplete obliteration of the lumen. There was a small area of mesenteric infarction, and a number of gastric erosions causing bleeding into the stomach. The cholecystoduodenostomy was patent. There was a solitary cyst in the head of the pancreas. The body and tail of the pancreas were atrophic, and the main pancreatic duct was dilated and ended blindly in the thick wall of the cyst. The area of the pancreas drained by the duct of Santorini was normal. The liver was hard; the surface was smooth, but showed red and grey mottling due to alternation of liver tissue and fibrous strands. The kidneys were normal apart from slight right hydronephosis.

TABLE I

Presenting Symptoms, Treatment, and Outcome

Patient	Age on presentation (years)	Mode of presentation	Age at which specific features were first noted: Hepatomegaly	Splenomegaly	Major gastrointestinal bleeding	Operative treatment	Age	Outcome (1959)
1	2½	Abdominal enlargement	2½	2½	Nil to date	Diagnostic laparotomy	2½	Alive. Retarded
2	6	Hepatosplenomegaly	6	6	Nil to date	Nil	..	Alive and well
3	5	Melaena	6	6	6	Portacaval anastomosis	6	Alive and well
4	3	Haematemesis	2	9	9	,,	12	Alive. Deteriorating
5	6	,,	6	6	6	,,	7	Alive and well
6	5	,,	5	5	5	,,	7	Alive and well
7	16	Anaemia	16	16	17	,,	21	Alive and well
8	2½	Abdominal enlargement	2½	3	Nil	Diagnostic laparotomy	2½	Died aged 4. Hepatic failure
9	2½	,,	2½	4	4	Portacaval anastomosis	5	Alive and well
10	5	Haematemesis	5	5	5	,,	5	Alive and well
11	2½	Hepatomegaly	2½	Nil	Nil	Nil	..	Died aged 2½. Septicaemia
12	8	Abdominal enlargement	8	8	10	Portacaval anastomosis	10	Alive and well
13	9	,,	9	9	14	Cholecysto-duodenostomy	14	Died aged 14. Portal and mesenteric thrombosis. Hepatic failure

Summary of Biochemical and Haematological Findings

The main findings are shown in Tables II and III. Pre-operative results are given as far as possible, as shunt operations may alter liver-function tests and haematological changes. The most striking feature is the normality of the findings in the face of gross hepatomegaly and usually portal hypertension. Serum bilirubin was definitely abnormal only in patient 8, who was found at

autopsy to have an abnormality of the large bile-ducts. She also showed the electrophoretic pattern of the serum proteins associated with biliary obstruction. In the other patients (except patient 13) the initial protein pattern was essentially normal. In patient 1 it has altered during the course of the illness, and in three others there was a decrease in serum albumin after haemorrhage or during infection. With one exception, flocculation tests gave consistently normal results. Serum transaminase levels in six patients were within the normal limits for the laboratory in which they were estimated. Bromsulphthalein excretion was normal in four out of five patients. The alkaline phosphatase level was consistently higher than the upper limit for the age-group in three patients, two of whom had abnormalities of mian bile-ducts. In five other patients it was high on one or more occasions.

Serum copper oxidase was estimated in seven patients, and was normal or increased in all seven. 'Sweat tests'—either the chloride-sensitive-plate screening test or measurement of sweat electrolytes—were carried out in seven patients, and gave normal results in all. Wassermann and Kahn reactions were negative in the five patients in which they were carried out. The comprehensive tests for blood-group incompatibility in patients 9, 10, and 11 are listed above; simple Rh incompatibility between mother and child was sought in four others; there was no evidence of incompatibility in any of the seven. Chromatography of the urine for amino acids was carried out in four patients; two gave normal results before operation. Patients 9 and 10 showed a general increase of all amino acids in the urine four years after portacaval anastomosis. Although isolated low white-cell counts and platelet counts were found in several children, only patients 12 and 13 consistently showed the pattern of normochromic anaemia, leucopenia, and thrombocytopenia associated with 'hypersplenism'. Both of these children had an unusually large spleen, which reached to the umbilicus. Bone marrow in patient 12 and in three others was normal or hyperactive. The one-stage prothrombin time was normal before operation in six patients, and slightly prolonged after operation in two others.

Histology of the Liver

Histological sections were available in all 13 cases, surgical biopsies in nine, needle biopsies in three, and post-mortem sections in two. In addition we have been privileged to examine sections from a further six cases not included in the present series, but mentioned in Table VII (Blakemore (1947), Case 3; van der Schoot (1955), Cases A and B; Hart-Mercer and Miller (1959), Cases 1, 2, and 3). The morphological changes were remarkably constant, and it will be convenient to describe the typical changes first and then to mention minor variations.

Typically the liver is divided up by bands of fibrous tissue (Plate 14, Fig. 1), varying from about 100 μ to 700 μ in thickness and sometimes reaching 1,000 μ. In seven cases these bands formed a continuous network enclosing liver-cell masses. In another four cases the network was less dense, and did not surround liver-cell masses; in the three needle biopsies it was not possible to tell. The

TABLE II

Biochemical Findings

Results marked with an asterisk were obtained after shunt operations. All other figures are the mean of pre-operative results.

Patient	*Serum albumin (g./100 ml.)*	*Serum globulin (g./100 ml.)*	*Electrophoretic pattern*	*Alkaline phosphatase (King–Armstrong units)*	*Serum bilirubin (mg./100 ml.)*	*Thymol turbidity (units)*	*Other flocculation tests*	*Serum cholesterol (mg./100 ml.)*	*Blood-urea*	*30 min. bromsulphthalein retention (%)*	*Serum transaminases SGOT (Sigma Frankel units)*	*Serum transaminases SGPT (Sigma Frankel units)*
1 *aet.* 18 months	4·4	1·9	Normal	64	0·3	14	Negative	309	..	..	..	..
aet. 30 months	2·4	5·1	Gamma increase	54	0·4	4	Negative	187	17	15	30	12
2	4·0	2·9	Normal	19	0·4	1	Negative	238	32	< 10	18	11
3	3·9	3·4	Normal	15	0·3	5	Negative	117	33	< 10*	25*	13*
4	4·9	2·1	Normal	9	0·4	..	Negative	..	..	..	..	..
5	5·0	2·1	Normal	9	..	2	..	..	..	..	..	..
6	4·2	3·3	Normal	12	0·2	4	Negative	..	30	< 10	..	..
7	4·3	3·0	..	6	0·3	4	Negative	..	..	..	..	..
8	3·9	3·8	Alpha-2, beta increase	57	1·5	4	Negative	261	..	..	..	..
9	4·3	3·0	Slight gamma increase*	9	0·5	5	Negative	272*	38*	..	15*	14*
10	3·5*	2·7*	Normal*	14	0·1	3	Negative	255*	40*	..	22*	11*
11												
12	4·3	3·3	Normal	42	0·7	2	Negative	250	37	< 10	30	18
13	3·6	3·9	Gamma increase	22	..	4	Negative	..	..	..	..	..

fibrous bands consisted of mature collagen with scanty fibrocyte nuclei, except in patient 1, where the fibrous tissue was still cellular, presumably owing to the patient's youth (one and a half years). Within the fibrous bands there was an obvious excess of bile-ducts, varying in size from well-formed tubular

TABLE III

Haematological Findings

Figures quoted are the mean of all estimations prior to surgery which were undisturbed by recent haemorrhage or infection. No such counts are available in patients 5 and 11.

Patient	*Haemoglobin (g./100 ml.)*	*Mean corpuscular haemoglobin concentration (g./100 ml.)*	*White cells (per cu. mm.)*	*Polymorphs (per cu. mm.)*	*Platelets (per cu. mm.)*	*Reticulocytes (%)*
1	11·0	31	19,000	8,500	191,000	2·7
2	11·4	35	3,400	1,700	155,000	1·2
3	12·9	32	13,000	8,000	130,000	..
4	11·4	..	..	..	..	..
6	16·0	..	5,000	3,000	314,000	..
7	..	..	8,000	6,000	..	..
8	13·4	..	8,500	2,900	..	..
9	10·2	..	4,300	2,600	50,000	..
10	10·4	..	9,200	7,100	200,000	..
12	10·9	32	2,000	1,100	90,000	0·8
13	12·7	..	2,800	1,500	34,000	..

structures of 150 μ diameter down to channels as small as 15 μ (Plate 14, Figs. 2, 3, and 4). There was never any evidence of proliferation in the form of mitoses, even among the small ducts. In three cases there was slight dilatation of some bile-ducts (Plate 14, Fig. 2) up to a maximal diameter of 600 μ, but never anything that could be called cystic change. In about half the cases (seven of 12) there was a tendency for the smaller bile-ducts to be concentrated at the edges of the fibrous strands (Plate 14, Fig. 3). In seven cases the bile-ducts contained small amounts of mucinous material visible in ordinary sections. In eight cases there were deposits of inspissated bile in the lumina, and in two cases (8 and 11) these were prominent features. The excessive number of bile-ducts was limited to the fibrous bands, only three cases showing any significant number among the liver cells (and these ducts lay between liver lobules). In Cases 2 to 9 inclusive we had material available to carry out special stains for the demonstration of bile canaliculi. In all eight of these cases the canaliculi were normal in size and distribution. Cellular infiltration of the fibrous strands was seen in six cases, being usually slight, diffuse, and lymphocytic. In one case it was focal. The junction between the liver-cell masses and the fibrous bands was always sharp, forming smooth lines (Plate 14, Figs. 2, 3, and 4). The liver cells appeared to be strictly normal except in Case 9, in which there was a little fresh centrilobular necrosis, probably attributable to ischaemia following a massive haemorrhage. The liver cells were arranged in regular columns of normal thickness (Plate 14, Figs. 1 and 2), and there was not the distortion of pattern that is seen in regeneration nodules. Liver lobular pattern was preserved in all cases in which the

TABLE IV

Evidence of Portal Hypertension and Collateral Circulation

(Positive observations are indicated by +, ++, or +++ according to severity; negative observations by O, and 'no observation made' by ..)

		Portal pressure (mm. Hg)			*Collateral Vessels*					
						Oesophageal varices				
Patient	*Splenomegaly*	*Intrasplenic*	*Operative*	*Hepatic vein wedged pressure*	*Abdominal wall veins**	*Barium swallow*	*Oesophago-scopy*	*Portal venogram*	*Other collaterals (portal venogram)*	*Intrahepatic pattern*
1	++	..	..	..	O	..	..	..	..	..
2	++	24	..	..	+	++	..	+++	Umbilical. Renal	Large portal veins show distorted pattern
3	++	18	..	..	+	++	..	+++	Pericardial. Parasplenic. Mesenteric	All contrast medium diverted through collaterals
4	++	..	25	..	..	++	..	++	O	Normal. Filled only when contrast medium injected into mesenteric vein
5	++	..	26	..	+	O	++	O	Umbilical	Normal
6	++	25	23	..	+	+	..	++	Hepatic capsular	Pattern distorted
7	+	..	19	..	..	..	..	..	..	..
8	++	35	..	..	+	O	..	O	O	Normal except for expansion in very large liver
9	++	..	30	19	+	..	+	+	O	Distorted. Slow emptying. Poor filling of peripheral veins
10	++	..	45	..	+	..	+	+	Inferior mesenteric	As patient 9
11	O	..	..	..	..	..	..	..	..	..
12	+++	..	..	..	+	O	..	+	Inferior mesenteric	Normal
13	++	..	39	..	O	++	..	++	O	Normal

* .. Indicates no record in notes. No patient had fully developed caput medusae or venous hum.

TABLE V

Macroscopic Appearances of Liver and Related Structures

Patient	*How organs were examined*	*Liver*					*Gall-bladder and large ducts*	*Portal vein*	*Regional lymph-nodes*
		Size	*Colour*	*Consistency*	*Surface*	*Cut surface*			
1	Operation	Grossly enlarged	Yellow	Very firm	Smooth	Homogeneous. Avascular	N.A.D.	N.A.D.	N.A.D.
2	Not seen	..	..	..	..	..	..	..	..
3	Operation	Slightly enlarged. Large caudate lobe	Normal pink	Firm	Fine fibrosis apparent, but no contracture of hepatic tissue between fibrous bands	..	N.A.D.	Small. < 1·25 cm. diam.	N.A.D.
4	Operation	Enlarged	Mottled	Firm	Smooth	..	N.A.D.	Normal	Many enlarged around portal vein
5	Operation	Normal size	..	Firm	Fine fibrosis	..	Gall-bladder distended, but otherwise normal	10 mm. diam.	Few enlarged, soft, around portal vein
6	Operation	Left lobe enlarged. Right lobe normal	Mottled pale and purple areas	Very firm	Smooth	..	Normal	Rather small. 10 mm. diam.	Few soft nodes around portal vein
7	Operation	Large	..	Hard	Some rather coarse nodules. Vascular adhesions	..	N.A.D.	Normal	N.A.D.
8	Autopsy	720 g. Left lobe small	Pale green	Firm	Large scar on right lobe. Fine nodularity elsewhere	Uniform fibrosis. Large bile-filled cavity in left lobe	Gall bladder and extrahepatic ducts normal. Blind-ended duct ran from cyst to hilum. Some dilatation of bile-ducts in right lobe	N.A.D	Enlarged throughout abdomen
9	Operation	Large	N.A.D.	Firm	'Cirrhotic'	..	Gall-bladder distended with bile. Otherwise normal	Normal	Increased around portal vein
10	Operation	Greatly enlarged	N.A.D.	Firm	'Fibrotic'	..	N.A.D.	Normal	Present around portal vein
11	Autopsy	Large. 1,080 g.	N.A.D.	Dense	Mild lobulation	Dense fibrosis	Normal	Normal	Many enlarged in porta hepatis and along superior border of pancreas
12	Operation	Greatly enlarged	N.A.D.	Dense	Left lobe enlarged, nodular. Right shrivelled	..	Large choledochous cyst	Normal	N.A.D.
13	Autopsy	Slightly enlarged	Mottled pink and grey	Very firm	..	..	Gall-bladder and common bile-duct dilated	Partly obliterated by thrombosis	N.A.D.

Note. 'N.A.D.' in this table signifies that the part was examined by the surgeon or pathologist and no abnormality was mentioned in the report. 'Normal' signifies that specific mention of the normality of the part was made in the operation note or autopsy report.

biopsy specimen was big enough for this to be ascertained. Lobular pattern in these cases refers to a regular radial arrangement of liver-cell columns around a central hepatic vein radicle.

The vasculature was interesting, and presumably relevant. Centrilobular hepatic veins were visible and appeared normal (Plate 14, Figs. 1, 2, and 4),

TABLE VI

Evidence of Polycystic Kidneys and other Urinary Abnormalities

		Appearance of kidneys		
Patient	*At operation*	*At autopsy*	*On intravenous pyelography*	*Other abnormalities*
1	Both normal	..	..	—
2	..	..	POLYCYSTIC	Urinary infection *aet.* 7
3	Right normal	..	Normal	Granular casts in urine
4	Right normal	..	..	—
5	Right normal	..	Calyceal pattern distorted on right. Not diagnostic of polycystic disease	—
6	Right normal	..	Normal	? Acute nephritis *aet.* 2
7	Right normal	..	..	—
8	—	Both normal	..	—
9	No comment made	..	Normal	—
10	No comment made	..	POLYCYSTIC	—
11	..	POLYCYSTIC	..	—
12	Right normal	..	Normal	—
13	Right normal	Slight right hydronephrosis	..	—

but larger radicles than this could not be recognized with any certainty. Hepatic arteries could be recognized in the fibrous bands, and their frequency and size per unit area of liver tissue was about the same as in control sections of normal liver; portal veins, on the other hand, were obviously scanty (Plate 14, Fig. 4; Plate 15, Fig. 5). In the majority of cases they were less frequent and no bigger than the hepatic arteries. In sections where the wider strands of fibrous tissue contained large hepatic arteries there were sometimes quite big portal veins, while small hepatic arteries often had no accompanying vein. It is possible that the paucity of portal veins affects only the more distal radicles, but we lack data on this point.

Discussion

Probably the first description of a patient suffering from portal hypertension complicating congenital cystic disease was by Bristowe (1856). He described briefly a man of 53 who died from congenital cystic kidneys, and who was found at autopsy to have a large cystic liver and a firm, non-cystic spleen

weighing 3 lb. There was no history of symptoms referable to portal hypertension. Although numerous case reports of congenital cystic liver and kidneys appeared over the next half century, all authors described the changes in the liver as interesting additional pathological findings rather than as an important cause of symptoms in life. Still (1898), reviewing the literature up to his time, found 35 cases of congenital cystic disease involving the liver, in none of which had the patient complained of symptoms referable to the liver. Many subsequent reviews have since appeared on non-parasitic cystic disease of the liver, with or without involvement of other organs (Moschcowitz, 1906; Beattie and Robertson, 1932; Davis, 1937; Norris and Tyson, 1947; Lambert, 1947; Comfort, Gray, Dahlin, and Whitesell, 1952; Sifre, Phelps, Cole, and Kimball, 1955; Melnick, 1955). These reviews, covering several hundred case reports, present cystic disease of the liver as a benign condition which affects prognosis only in as much as it is often associated with the more serious involvement of the kidneys. The disease seldom leads to surgical intervention, and most operations are carried out for pain following haemorrhage into a cyst or gross enlargement of the liver. Henson, Gray, and Dockerty (1957) described 29 such patients, none of whom had any evidence of portal hypertension. One death from bleeding oesophageal varices was recorded by Rall and Odel (1949) in a review of 207 cases of congenital cystic disease from the Mayo Clinic, but no complications attributable to portal hypertension were recorded by any of the other authors listed above.

In the majority of reported cases the liver has contained cysts of various sizes, visible to the naked eye. Several authors, however, have pointed out that the predominant changes in the liver in some patients are fibrosis and microscopic abnormalities of interlobular bile-ducts, and that these may be present in the absence of large cysts. Good descriptions of the microscopic pathology in patients with visible cysts were given by Bristowe (1859), Komorowski (1876), Demantké and Fournier (1895), and Claude (1896). Still (1898), Couvelaire (1899), Moschcowitz (1906), Bunting (1906), and Royster (1918) all described infants who died at birth or in the first year of life with congenital cystic kidneys, and who showed only microscopic changes in the liver. Bunting's patients were two siblings, both of whom had splenomegaly. The liver in these infants was sometimes smooth, but in two cases it had a superficial appearance resembling cirrhosis; Couvelaire (1899), describing one of these cases, commented: 'Les seules lésions apparentes a l'oeil nu dans cette organe peuvent consister aimplement en une hypertrophie cirrhotique.' The similarity between the gross appearance of this lesion and that of cirrhosis has certainly led to the misdiagnosis of some patients with congenital cystic disease.

The existence of this form of 'cystic liver *sine* cysts' received scant recognition for the next 40 years. MacMahon (1929) gave a description of the condition in a classification of congenital anomalies of the liver, and recalled its frequent association with congenital cystic kidneys. He commented on the extremely regular cuboidal lining of the abnormal interlobular bile-ducts. In a later review MacMahon (1955) described the condition of 'congenital hyperplasia of

interlobular bile ducts' as a relatively common anomaly associated with cysts of the liver, kidney, and pancreas, and occasional abnormalities of the portal vein. In 1952 Dustin, describing the pathology of 'Banti's syndrome', cited the case of a nine-year-old boy with splenomegaly and haematemesis, in whom sections of the liver showed changes that we would now classify as those of congenital hepatic fibrosis, without evidence of cystic disease elsewhere. Two similar cases were described by Grumbach, Bourillon, and Auvert (1954). Parker (1956) described the characteristic lesion in the liver in six patients at autopsy. In two, who had lived beyond childhood, symptoms of portal hypertension had been present in life. Krainer (1957) described the same pathological picture in biopsy specimens from four young adults with portal hypertension, three of whom also had congenital cystic kidneys. Campbell, Bick, Paulsen, Lober, Watson, and Varco (1958) described a family of three children who all suffered from portal hypertension, congenital hepatic fibrosis, and cystic kidneys. Ivemark, Oldfelt, and Zetterström (1959) described two siblings with the same pathological picture who died from uraemia, but in whom portal hypertension was absent. We have been fortunate in having the opportunity to examine histological specimens from three patients who have been described as suffering from portal hypertension due to cirrhosis with congenital cystic kidneys (Blakemore, 1947; van der Schoot, 1955). All three proved to have the changes typical of congenital hepatic fibrosis. The main findings in previously described cases, including these three, are summarized in Table VII.

The commonest mode of presentation is gastrointestinal haemorrhage from oesophageal varices, but hepatomegaly and splenomegaly are usually present from an early age, and are sometimes found on routine examination many years before the onset of haemorrhage. Hepatomegaly has been found before the age of three years in five of our patients, and it was present at birth in some of those quoted from the literature. In one of the present series, however, it was looked for and not found up to the age of two and a half years, so that it is possible that the liver sometimes enlarges during growth. The large size of the liver is a helpful diagnostic point; it was great enough to cause striking abdominal protuberance in five of our patients; it contrasts with the small liver often found in cirrhosis. The other outstanding feature of the liver is its extreme toughness. This is usually obvious on physical examination, it often causes comment at operation, and it is particularly noticeable when needle biopsy of the liver is attempted.

Hepatic failure, with ascites and coma, can complicate congenital hepatic fibrosis, usually after haemorrhage. It is, however, uncommon, and the general well-being of the patients, their lack of jaundice, and their good liver function (clinically and on biochemical testing) are in clear contrast to the usual findings in cirrhosis. Our own experience of the last four years suggests that, if a British child with gross hepatomegaly and portal hypertension has no jaundice or ascites, and gives normal results on liver-function tests, the likeliest diagnosis is congenital hepatic fibrosis. A raised level of serum alkaline phosphatase is compatible with the diagnosis, but introduces the possibility of

TABLE

Summary of Patients described by Previous Authors,

(+ = positive observation; 0 = negative

Author	*Case number*	*Age (years)*	*Mode of presentation*	*Sex*	*Hepato-megaly*	*Splenomegaly*	*Gastrointestinal bleeding*	*Jaundice*	*Ascites*	*Hepatic coma*	*Portal hypertension*
Dustin (1952)	2	9	Splenomegaly	M	+	+	*aet.* 9	Slight	0	0	Presumed
Grumbach, Bourillon, and Auvert (1954)	1	1	Hepatomegaly	M	+	+	*aet.* 5	0	*aet.* 5	0	36 mm. Hg
	2	8	Hepatomegaly	M	+	*aet.* 11	*aet.* 17	0	0	0	36 mm. Hg
Parker (1956)	1	At birth	Neonatal death	F	+	0	0	0	0	0	..
	2	At birth	Neonatal death	F	+	+	0	0	0	0	..
	3	8	Street accident	M	0	0	0	0	0	0	..
	4	33	Uraemia	M	0	0	0	0	0	0	..
	5	11	Abdominal enlargement	F	+	+	0	0	*aet.* 16	*aet.* 16	Presumed
	6	33	Haematemesis	M	+	+	+	0	0	*aet.* 33	Presumed
Campbell, Bick, Paulsen, Lober, Watson, and Varco (1958)	1	14	Haematemesis	F	+	+	+	0	0	0	27 mm. Hg
	2	15	Haematemesis	F	+	+	+	0	0	*aet.* 15	30 mm. Hg
	3	25	Haematemesis	M	+	+	+	0	0	0	Present
Krainer (1957)	1–4	Young adults	..	..	..	..	..	..	..	..	Present
Blakemore (1947)	3	5	Haematemesis	F	..	..	+	0	0	0	Present
van der Schoot (1955)	A	13	Splenomegaly	F	0	+	*aet.* 49	0	0	0	Presumed
	B	15	Splenomegaly	F	0	+	0	0	*aet.* 44	0	Presumed
Ivemark, Oldfelt, and Zetterström (1959)	1	$\frac{1}{12}$	Uraemia	F	+	0	0	Slight	0	0	..
	2	$\frac{3}{12}$	Uraemia	M	+	+	0	+	0	0	..
Hart-Mercer and Miller (1959)	1	12	Haematemesis	F	+	+	+	0	0	0	Presumed
	2	6	Haematemesis	F	+	+	+	0	0	0	Presumed
	3	9	Abdominal enlargement	M	+	+	+	0	0	0	Presumed

VII

now regarded as Cases of Congenital Hepatic Fibrosis

observation; .. = not recorded, or inapplicable)

Splenogram	*Liver-function tests*	*Haematology**	*Polycystic kidneys*	*Other anomalies*	*Operative treatment*	*Subsequent course*
..	Normal	Leucocytosis. Thrombocytopenia	0	0	Splenectomy	Survived operation. No follow-up
Oesophageal varices. Normal intrahepatic pattern	..	Leucopenia	0	Obstruction to common bile-duct	Spleno-renal anastomosis	Post-operative cholecystitis and fatal biliary peritonitis
Normal. Varices on barium swallow	..	Anaemia. Leucopenia	0	Dilated gall-bladder	Spleno-renal anastomosis	Recovery. No follow-up
..	..	..	+	0	..	Death from asphyxia within half hour of birth. Autopsy showed C.H.F. and large polycystic kidneys
..	..	..	+	Meningoencephalocele. Cleft palate. Dislocated toes	..	Death at 1½ hrs. Autopsy showed C.H.F. and multiple congenital anomalies
..	..	..	+	0	..	Chance finding of C.H.F. and polycystic kidneys at autopsy
..	..	..	+	Stones in gall-bladder and intrahepatic bile-ducts	..	Death from uraemia
..	..	Normal	0	Pyelonephritis	..	Death from perinephric abscess with terminal coma
..	..	Normal	0	Hydronephrosis	..	Death from primary bile-duct carcinoma with terminal coma, following haematemesis
..	Normal	Normal	+	..	Spleno-renal anastomosis	Bled again 9 months later; portacaval anastomosis. Well since
..	Normal	Normal	+	0	Portacaval anastomosis	Well since operation
Oesophageal varices. Poor filling of liver	Albumin low after operation	Leucocytosis after operation	+	0	Spleno-renal anastomosis	Recurrent haemorrhage treated by total gastrectomy and oesophageal transplant. Fatal septicaemia
..	..	..	+ in 3	Small portal vein in one	..	..
..	Normal	..	+	..	Spleno-renal anastomosis	Shunt became occluded. Died 2 years later of uraemia
..	Normal	..	+	..	Laparotomy. Splenectomy *aet.* 18	Remained well for 36 years after splenectomy. Died one day after laparotomy for haematemesis, *aet.* 49
..	..	..	+	Aneurysms of R. renal and R. middle cerebral arteries	..	Death *aet.* 46 from subarachnoid haemorrhage
..	Alpha-2 globulin increase	Haemolytic anaemia	+	Cystic dysplasia of pancreas. Rickets	..	Death from uraemia
..	Bilirubin 13 mg./100 ml.	Leucocytosis	+	Cystic dysplasia of pancreas	..	Death from uraemia
Oesophageal varices	Alkaline phosphatase raised. Weakly + flocculation tests	..	0	0	Portacaval anastomosis *aet.* 13	Alive
..	..	..	0	0	..	Died from haematemesis
..	Alkaline phosphatase raised	Normal	0	0	Splenectomy, oesophageal devascularization *aet.* 9	Alive

* Anaemia following haemorrhage is ignored.

C.H.F. = congenital hepatic fibrosis

associated anomalies of the large bile-ducts. In the above circumstances a search should be made for congenital cystic kidneys, especially by intravenous pyelography. Their presence makes the diagnosis of congenital hepatic fibrosis almost certain, as the usual form of congenital cystic liver rarely causes portal hypertension. In the absence of demonstrable cystic kidneys a positive diagnosis can be made only by adequate liver biopsy. The characteristic features may be seen in a needle biopsy specimen, but the preservation of lobular architecture can be recognized with certainty only by surgical biopsy. The use of a reticulin stain is of great help in displaying lobular architecture. Aspiration needle biopsy has proved very difficult in these patients; the biopsy specimen is liable to fragmentation, leaving only small pieces of apparently normal liver. Good specimens have been obtained on three occasions with the Vim Silverman needle.

Aminoaciduria in some patients with congenital hepatic fibrosis may lead to initial confusion with Fanconi's syndrome. The respiratory abnormalities and alterations in sweat electrolytes found in pancreatic fibrosis are not seen. The Kayser–Fleischer corneal rings and fall in serum copper oxidase levels characteristic of Wilson's disease are not found in congenital hepatic fibrosis.

The prerequisites for successful surgical relief of portal hypertension by shunting operations are adequate liver function and a patent portal vein of normal size. Since these are present in most patients with congenital hepatic fibrosis they should stand surgery well, and this view is confirmed by the results of portacaval anastomosis in eight of our patients. All survived the operation, and the shunt has remained patent in seven without further bleeding. After a second operation in the eighth patient, all have done well for an average follow-up period of nearly three years. The unfavourable results in some previously reported patients, after the less satisfactory operations of splenectomy and spleno-renal anastomosis, do not invalidate our conclusion that such patients usually do well. In the past the unusual character of the lesion has been recognized only if the patient came to autopsy, and unsuccessful operations have therefore been given undue prominence. Two of our patients, and one previously described, have suffered from septicaemia; it may be that these, like cirrhotic subjects, are unusually susceptible to this complication.

Thirteen of the 24 previously recorded patients had polycystic kidneys, and three had other forms of renal disease (Table VII). Four infants died in the neonatal period, partly or entirely because of their polycystic kidneys, but of those who survived the first month of life only two died from uraemia, at seven and 33 years of age respectively. This is in accord with the usual behaviour of cystic kidneys, which tend to cause symptoms in infancy or after the age of 40. The lower incidence of polycystic kidneys in our own series (three out of 13 patients) is probably explained by their age and the selection of cases; all but one came to our notice because they attended centres concentrating on the treatment of liver disease, and 10 are still alive between the ages of three and 22 years. Less than half of all patients with polycystic kidneys present symptoms before the age of 50 (Dalgaard, 1957), and their detection before that age, even

with the aid of pyelography, may be difficult. It may well be that more of our patients will eventually prove to have renal involvement.

Five of our patients had anomalies of the main bile-ducts and gall-bladder. None of these five patients had been jaundiced prior to their first liver biopsy, and the histological picture was quite distinct from that of biliary cirrhosis. Three previously reported patients have had similar abnormalities of the biliary tree, and congenital anomalies of other organs have occasionally been recorded (Table VII).

Aetiology. The histological and clinical evidence so clearly points to congenital hepatic fibrosis being a variant of congenital cystic disease that a genetic basis for the illness is an obvious assumption. The inheritance of polycystic disease of the usual type has been exhaustively reviewed by Dalgaard (1957). The familial form of this disease is probably transmitted as a Mendelian dominant of very high penetrance (approaching 100 per cent.) but very variable expressivity. Many sporadic cases occur, however, in which there is no family history. There is insufficient information on the family histories of patients with congenital hepatic fibrosis to construct any theory of its inheritance. Most of the previous case reports contain no mention of the families. The three patients described by Campbell, Bick, Paulsen, Lober, Watson, and Varco (1958) were a brother and twin sisters; there were no unaffected siblings. Van der Schoot's (1955) two patients were also sisters; an elder sister died at the age of 13 from haematemesis, and it is probable that she was also affected by the same illness. Again there were no unaffected siblings. Patients 9, 10, and 11 in our own series form a similar sibship, all three being affected. Ivemark, Oldfelt, and Zetterström's (1959) two patients were brother and sister; there was a third sibling of whom no details are given. Two of Hart-Mercer and Miller's (1959) patients were brother and sister, without any unaffected siblings. In none of these cases was there any known consanguinity between the parents, nor was there any history suggestive of the illness in previous generations. These family histories are compatible with either a recessive mode of inheritance or a dominant mode following mutation of a gene. Study of the families of four of our other patients has shown that the eight parents, and six elder and seven younger siblings, are all unaffected as judged by history and physical examination. Liver-function tests gave normal results in the seven siblings tested. In none of the families was there any consanguinity between the parents, or any history suggesting the disease in previous generations. A comparison of the familial and non-familial patients in our own and previous series reveals only one important difference; in 10 of the 13 familial cases the patients had associated congenital cystic kidneys, compared with six of the 22 non-familial cases (Parker's (1956) Case 5 is not included, as the patient may have had an affected sibling).

Since the present paper was prepared a family of three children has been studied, of whom two have typical congenital hepatic fibrosis and cystic kidneys, and the middle child is normal clinically and on intravenous pyelography

and liver biopsy. No cases have been discovered in the previous generation. This is in keeping with a recessive mode of inheritance.

Pathogenesis of the portal hypertension. Portal hypertension in cirrhosis of the liver is variously attributed to compression of small hepatic veins by regeneration nodules (Kelty, Baggenstoss, and Butt, 1950; Popper, Elias, and Petty, 1952; Popper and Elias, 1955), excessive arteriovenous communications in the liver (Herrick, 1907; Dock, 1942; Berman and Hull, 1953), or reduction in the portal vein bed (McIndoe, 1928). It is associated with gross distortion of the fine architecture of the liver. Since the lobular architecture is usually well preserved and regeneration nodules are not present, the cause of portal hypertension in congenital hepatic fibrosis is less obvious. A congenitally small portal vein was present in one of Krainer's (1957) patients, but the main portal vein has been visualized at operation, at autopsy, or on a portal venogram in 12 of our patients and in at least 18 of the previous cases, and has not been hypoplastic except, perhaps, in our patient 3. The intrahepatic pattern of larger portal veins has been displayed by venography in nine of our patients and in two previous ones; it was normal in seven, and distorted, as in cirrhosis, in the remaining four. In two of our patients, and probably in a third, there was a distinct paucity of finer branches in the periphery of the liver; this was true of all the films taken, though it is impossible to be sure that these branches were not filled at some time between exposures. It was thought that in these patients the portal phase of the splenic venogram was excessively long, suggesting slow emptying of the portal vein into the sinusoidal bed; but exact timing of the phases was not practised. We conclude that macroscopic branches of the portal vein may be defective in a proportion of patients, but it is unlikely that this is the usual cause of the portal hypertension.

The histological evidence of portal vein hypoplasia is more convincing. MacMahon (1955) stated that 'congenital hyperplasia of interlobular bile ducts' was associated with a defect in the development of the portal system of veins within the liver, and Grumbach, Bourillon, and Auvert (1954) commented that portal vein radicles were difficult to see in the liver sections of their patients. Both portal vein radicles and smaller hepatic arteries—especially the latter—were defective in one of Parker's cases, but not apparently in the other five. On the other hand, Campbell, Bick, Paulsen, Lober, Watson, and Varco (1958) thought that portal vein radicles were, if anything, more numerous than normal. We have compared the number of portal vein radicles in the surgical and autopsy specimens from our patients and those of Blakemore (1947) and van der Schoot (1955) with control sections of normal liver, and have found a striking lack of smaller portal vein branches which we think is sufficient to account for the occurrence of portal hypertension. Some collateral evidence on this point might be obtained from further investigation. Wedged hepatic vein pressure is thought to measure the post-sinusoidal resistance, and in cirrhosis is usually close to the portal pressure, suggesting that most of the obstruction is in the hepatic veins (Myers and Taylor, 1951; Paton, Reynolds, and Sherlock, 1953;

Atkinson and Sherlock, 1954). It should be considerably lower than portal pressure measured in the spleen or directly in the vein in patients with congenital hepatic fibrosis, if the portal hypertension is in fact due to pre-sinusoidal obstruction. So far the only recorded measurement of wedged hepatic vein pressure in this condition is in our patient 9, and unfortunately it is not strictly comparable with the portal vein pressure, which was carried out on a different occasion during operation. As far as it goes, the difference in pressure between the two readings supports our theory, but a divergence as great as this is occasionally encountered in cirrhosis. Hepatic vein catheterization in children is not usually practised because of radiation exposure and the necessity for an anaesthetic, but with the aid of the image intensifier it should now be possible to carry out the procedure immediately before surgery.

The authors wish to express their thanks to the physicians and surgeons who referred patients described in this paper, for access to their case records; particularly to Dr. W. P. Sweetnam and Mr. Geoffrey Wooler, for information about patients 9, 10, and 11; to Dr. Blakemore, Dr. van der Schoot, and Professor Dupont, who kindly lent histological slides from patients previously described by them, for permission to include some of their patients in the review of the literature under a new title; to Dr. F. J. W. Miller and Dr. J. Hart-Mercer, for permission to include details of their unpublished cases in Table VII; to Dr. Steiner, Dr. Laws, and Dr. Ross, for reporting the portal venograms; and to Sister Card, Sister Barrett, and their nursing colleagues for care of the patients in Hammersmith Hospital and Bristol Royal Infirmary.

Summary

Congenital hepatic fibrosis is a condition related to congenital cystic liver, and often associated with polycystic kidneys. It is a cause of hepatomegaly and portal hypertension in children and young adults which should be distinguished from cirrhosis and similar diseases, since liver function is well preserved, and the patients are good candidates for surgical relief of portal hypertension.

The criterion of diagnosis is the characteristic histological picture seen in liver biopsy sections. Clinical features which suggest congenital hepatic fibrosis include gross enlargement and very firm consistency of the liver, and the presence of other congenital anomalies. Serum proteins, bilirubin, transaminases, flocculation tests, and bromsulphthalein retention are usually normal, but plasma alkaline phosphatase levels are sometimes elevated.

The disease sometimes affects two or more siblings, but has not yet been reported in successive generations.

A deficiency in the terminal branches of the portal vein is thought to be responsible for the portal hypertension.

Twenty-four previous cases are reviewed, and 13 new cases added.

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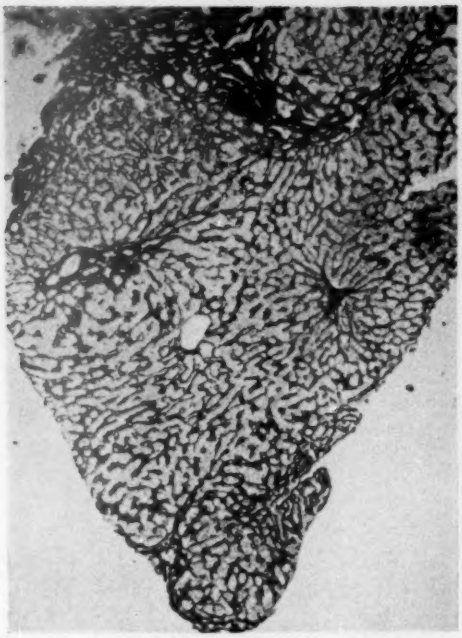

FIG. 1. Patient 7. The normal lobular architecture is preserved. There is a band of fibrous tissue containing many bile-ducts at the top of the picture. (Silver impregnation for reticulin fibres, ×55)

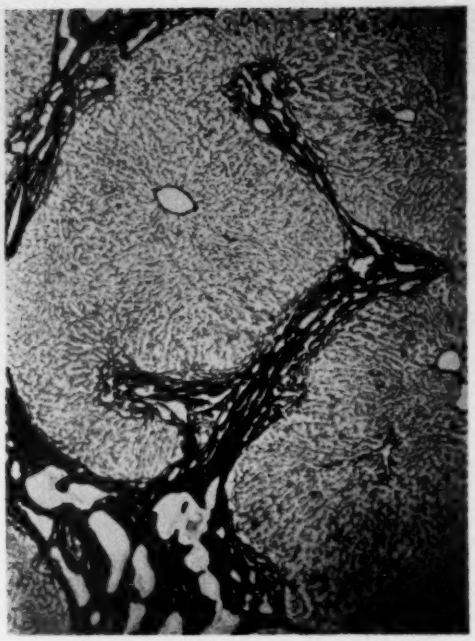

FIG. 2. Patient 5. Broad bands of fibrous tissue containing bile-ducts separate and surround liver lobules. (Silver impregnation, ×36)

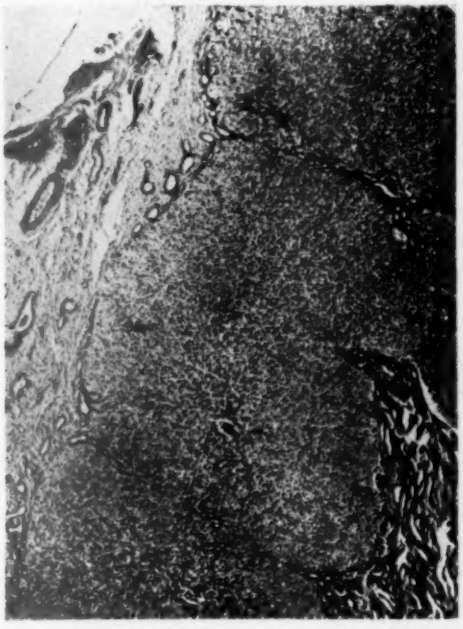

FIG. 3. Patient 6. Healthy liver lobules lie between bands of dense fibrous tissue containing many bile-ducts and a hepatic artery (top left). Note the absence of portal vein radicles. (Haemalum and eosin, ×40)

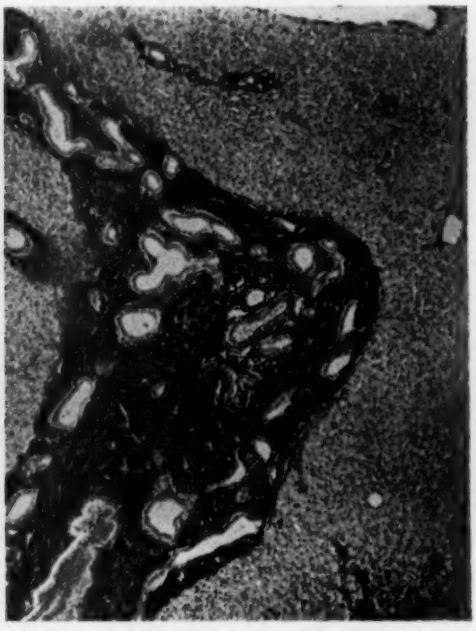

FIG. 4. Patient 4. Broad fibrous band containing a hepatic artery (arrow) and many bile-ducts, but no portal vein. (Elastic, van Gieson, ×50)

FIG. 5. Patient 3. Fibrous band showing a presumptive portal vein (thin dark wall) next to a hepatic artery. (Elastic, van Gieson, ×50)

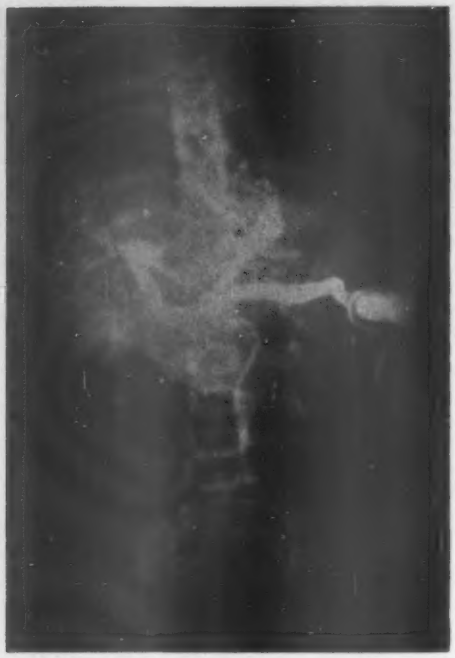

FIG. 6. Patient 10. Trans-splenic portal venogram. Collateral circulation outlined through the inferior mesenteric and left gastric veins; the portal vein and proximal branches well filled, but possibly deficient filling of peripheral vessels

FIG. 7. Patient 4. Trans-splenic portal venogram. Parasplenic collateral vessels filled, but no contrast medium entering the splenic and portal veins

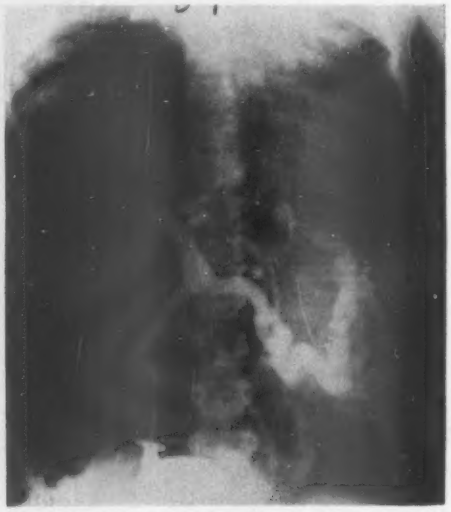

FIG. 8. Operative mesenteric venogram. Portal vein well filled; retrograde filling of splenic and collateral vessels

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FAMILIAL CARDIOMYOPATHY[1]

By A. G. W. WHITFIELD

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With Plates 16 to 21

Isolated disease of the heart muscle or cardiomyopathy is within the experience of most general physicians, and is a familiar problem to the cardiologist. In some instances there is no clue as to the aetiology, but in others the cause appears to be partly or wholly identifiable. Endomyocardial fibrosis probably comprises the largest group (Arnott, 1959), and in this condition some factor arising from residence in Africa appears to be responsible, as the recorded cases have been in Africans (Bedford and Konstam, 1946; Ball, Williams, and Davies, 1954; Davies and Ball, 1955), Arabs in the Sudan (O'Brien, 1954), and Europeans who have lived for a long time in Nigeria (Edge, 1946; Gray, 1951). In the Occident alcoholism is probably the most important single cause (Blankenhorn, Vilter, Scheinker, and Austin, 1946; Benchimol and Schlesinger, 1953; Brigden, 1957; Evans, 1959), while amyloidosis (Benson and Smith, 1956; Brigden, 1957) and infections account for many of the remainder. Of the infections, diphtheria is today a rarity, and most of the reported cases in which it has been possible to identify the infective agent have been due to the influenza virus (Finland, Parker, Barnes, and Joliffe, 1945; Borden, 1950), the Coxsackie virus (Javett, Heymann, Mundel, Pepler, Lurie, Gear, Measroch, and Kirsch, 1956), toxoplasmosis (Bengtsson, 1950; Paulley, Jones, Green, and Kane, 1956), trichiniasis (Spink, 1935), trypanosomiasis (Chagas' disease), or tuberculosis (Benchimol, Carneiro, and Schlesinger, 1959). Cardiomyopathy occurs as a post-partum phenomenon (Gouley, McMillan, and Bellet, 1937; Meadows, 1957; Brigden, 1957; Rosen, 1959), and in some cases toxaemia of pregnancy appears to have played a part (Benchimol, Carneiro, and Schlesinger, 1959). Myocardial involvement is also seen in the collagen diseases, but not often as the presenting feature. An appreciable number of cases of cardiomyopathy appear to be familial (Evans, 1949; Davies, 1952; Paulley, Jones, Green, and Kane, 1954, 1956; Gaunt and Lecutier, 1956; Campbell and Turner-Warwick, 1956; Brigden, 1957). The present communication describes another family in which many of the members are suffering or have died from cardiomyopathy, and endeavours to examine the condition more closely than has been done heretofore.

The first member of the family to be seen was a young married woman of

[1] Received March 28, 1960.

23 years (Case 1), who was referred by her general practitioner in August 1957 for an opinion as to the safety of further childbearing. She had been breathless on exertion since childhood, and particularly so during her only pregnancy three years previously. She had no other symptoms, and there was no history of rheumatism or other significant illness. The heart was of 'mitral' shape, but

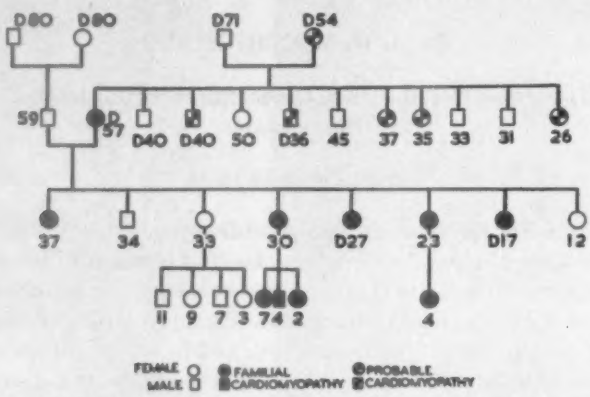

FIG. 1. Family pedigree showing affected and unaffected members. The numbers show their ages (D = at death). The five affected members of the proposita's generation, in order of age, are Cases 5, 6, 2, 1 (the proposita), and 4.

not enlarged, and loud gallop rhythm and a grade 2 pulmonary systolic murmur were audible. The blood-pressure was normal, and there was no abnormality of the lungs, and no anaemia. The electrocardiogram showed left ventricular dominance. The nature of the cardiomyopathy was not appreciated until she told us of the deaths from heart failure of an older sister (Case 2) and of her mother (Case 3), both of which occurred in the autumn of 1958. Dr. J. H. Sheldon and Dr. E. J. Blair, under whose care the sister and mother were, very kindly allowed us access to their case notes, from which it was apparent that they had suffered and died from a form of cardiomyopathy similar to that which our patient presented. It thus appeared highly probable that the cardiomyopathy was of the familial type, and, when this was explained to the patient and her husband, she told us of a younger sister (Case 4) who had been breathless on exertion for many years and had died suddenly from heart failure while cycling to hospital for consultation. We were also asked to see the patient's daughter (Case 10) who, though apparently well, has a 'mitral-shaped' heart and an abnormal electrocardiogram. Thereafter numerous other members of the family sought our advice, and our findings are summarized in Fig. 1, from which it will be seen that two other sisters (Cases 5 and 6) and all the children of one of them (Case 6) (Cases 7, 8, and 9) are also affected, while the remaining two sisters and the four children of one appear to be quite normal. We have not been able to see any of the maternal aunts or uncles of our original patient, but two of the uncles died suddenly from heart failure (Cases 11 and 12) and three of the aunts (Cases 13, 14, and 15) have had 'heart trouble' for many years,

while the maternal grandmother (Case 16) 'always had a bad heart', and died at the age of 54 after three months in bed with heart failure. The detailed case protocols of the affected members of the family are given in the Appendix.

1. *Symptoms.* The symptomatology of all the affected members of the family of whom we have authentic information is summarized in Table I, from which it will be seen that dyspnoea on exertion and cardiac pain have been the most prominent subjective features. Palpitation was complained of by two of the patients. Embolic phenomena occurred in two, one of whom had auricular fibrillation and the other a[illegible]tter. Congestive cardiac failure occurred in two patients as a termi[illegible]nenon, and one of these had a previous episode of failure during pregnancy. Sudden death occurred in one patient (and in two others of whom we have incomplete information). None of the four child patients had symptoms.

Dyspnoea on exertion was present in five of the patients. In two it had been present since childhood, and in two others it was first noticed in early adult life; in the fifth it had been evident for many years and, as she died at the age of 17, it must have developed in childhood, but there is no exact information as to when it was first noticed. In all cases it appears to have been increasingly troublesome as the years have gone by, but one patient (Case 6) noticed a considerable variability in her exercise tolerance from time to time. In the three patients who have borne children the dyspnoea seems to have been very much worse during pregnancy. In the four children affected even vigorous physical activity did not appear to provoke any undue dyspnoea.

Cardiac pain was a symptom in three of the patients. It was a late feature, appearing after dyspnoea on exertion had been present for many years. The pain seemed typically anginal, both in its distribution and in that it was provoked by exertion and by emotional disturbance. An unusual feature, however, was its duration: in one of the patients it lasted for an hour, and in another for two hours or more. Nitroglycerine appeared to relieve it.

Palpitation. In one of the two patients who complained of palpitation (Case 6) short bursts of regular tachycardia, at a rate of 140 per minute, were occasionally observed during examination, suggesting that the symptom was due to a paroxysmal arrhythmia, but it has not been possible to obtain any electrocardiographic confirmation of this. In the other patient (Case 5) attacks of palpitation were sometimes provoked by exertion or excitement, and at other times occurred without obvious cause. Her electrocardiographic records and physical examination never showed anything but sinus rhythm. In both patients the symptom was of long standing, showing itself first at about the same time as dyspnoea on exertion.

Embolic phenomena occurred in two patients. In one (Case 2) pulmonary and renal infarcts occurred, and in the other (Case 3) a left femoral embolus necessitated amputation of the leg, and an abdominal embolus may have occurred previously. Both patients had abnormal cardiac rhythms at the time

TABLE I

Symptoms

Case number	*Sex*	*Age (years)*	*Alive or dead*	*Number of children*	*Dyspnœa on exertion*	*Cardiac pain*	*Palpitations*	*Embolic phenomena*	*Cardiac failure*	*Sudden death*
1	F	23	A	1	Since childhood	None	None	None	None	..
2	F	27	D	2	Since childhood	2 years	None	Pulmonary and renal	During 2nd pregnancy and terminal	..
3	F	57	D	8	None	None	None	Femoral	Terminal	..
4	F	17	D	0	Many years	None	None	None	None	While cycling to hospital for consultation
5	F	37	A	0	18 years	2 years	18 years	None	None	..
6	F	30	A	3	11 years	1 year	9 years	None	None	..
7	F	7	A	0	None	None	None	None	None	..
8	M	4	A	0	None	None	None	None	None	..
9	F	2	A	0	None	None	None	None	None	..
10	F	4	A	0	None	None	None	None	None	..
									(Also Case 16) terminal	(Also Cases 11 and 12)

TABLE II

Objective Abnormalities

	Heart size		*Heart shape*			
Case number	*Enlargement*	*Cardio-thoracic ratio (%)*	*Postero-anterior radiograph*	*Screening*	*Murmurs*	*Gallop rhythm*
1	None	48	Mitral	Suggesting mitral stenosis	Grade 2 pulmonary systolic	Present
2	Present	59	Mitral	Not done	Systolic murmur when 17. Disappeared later	None
3	None	Not known	Mitral	Right ventricle enlarged	None	None
5	Present	53	Pear-shaped	Suggesting mitral stenosis	Grade 2 systolic inside mitral area	Present
6	Present	51	Mitral	Diffuse enlargement	Grade 2 pulmonary systolic	None
7	Present	52	Mitral	Diffuse enlargement	Grade 2 mitral systolic	None
8	None	50	Mitral	Normal	Grade 3 pulmonary systolic	None
9	Present	58	Suggesting left ventricular enlargement	Not screened	Grade 3 basal systolic	None
10	Present	57	Mitral	Diffuse enlargement	None	None

during which the embolic incidents occurred, the former being in flutter with irregular ventricular response and the latter having auricular fibrillation.

Congestive cardiac failure. Two patients were in congestive cardiac failure as a terminal phenomenon. In one (Case 3) failure was present for five weeks before death, and in the other (Case 2) for three months. The latter patient also had a protracted episode of congestive failure during her second pregnancy, two years before her death. She was in hospital for five months on this account, and labour had to be induced at the 32nd week. Thereafter failure was rapidly relieved.

A further patient (Case 16) is also stated to have been in bed for three months with congestive cardiac failure before her death.

Sudden death occurred in three cases. One of the patients (Case 4) died at the age of 17 while cycling to hospital for consultation, and the coroner's autopsy showed death to be due to heart failure resulting from chronic myocarditis. Two others (Cases 11 and 12) are also stated to have died suddenly from heart failure, the former at the age of 36 while riding his bicycle to work, and the latter while returning to England aboard ship.

2. *Objective abnormalities.* The chief findings are summarized in Table II. Cardiac enlargement, a 'mitral' configuration of the heart, systolic murmurs, and in two instances gallop rhythm, were the most striking features. The blood-pressure was normal in all patients, and none of them showed any abnormality outside the cardiovascular system. (No information is available regarding the physical signs presented in Cases 4 and 11 to 16, and these are therefore excluded.)

Heart size and shape. Of the nine patients in whom the necessary information is available, cardiac enlargement was present in six and absent in three. In none of the six was the enlargement gross, the highest cardio-thoracic ratio being 59 per cent. On the ordinary postero-anterior chest radiograph the straight left border of the heart shadow suggested mitral disease in seven instances, while in one (Case 9) the appearances were of left ventricular hypertrophy, and in the remaining one (Case 5) the heart appeared pear-shaped. In two instances (Cases 1 and 5) screening also suggested mitral stenosis, while in one (Case 3) it showed right ventricular enlargement; in three others the enlargement appeared to be diffuse rather than due to the involvement of any particular chamber.

Auscultatory findings. In none of the patients was there a palpable thrill, and in two no murmurs were audible. One (Case 2) had a systolic murmur which led to a diagnosis of ventricular septal defect when she was 17 years old, but no murmurs were audible eight and 10 years later. The remaining six patients had grade 2 or grade 3 systolic murmurs, loudest in the pulmonary area in three instances, in the mitral area in two, and at the base in one. Gallop rhythm was audible intermittently in two patients.

3. *Electrocardiographic findings.* All the nine patients who had electrocardiographic examination showed abnormal tracings (Table III). One (Case 2)

showed auricular flutter, and one (Case 3) showed auricular fibrillation. The remaining seven had sinus rhythm. The most unusual abnormality was seen in the P waves, which in six instances were unusually large and either pointed or bifid. The P-wave changes were most frequently seen in the standard leads

TABLE III

Electrocardiographic Findings

Case number	*Rhythm*	*Q waves*	*Abnormal P waves*	*Abnormal T waves*
1	Sinus	None	II, VF	I, II, III, VR, VL, VF, V5, V6
2	Auricular flutter	None	None	None
3	Auricular fibrillation	None	None	I, II, III, VL, VF, V3–V7
5	Sinus	None	I, II, III, VR, VF, V2–V6	I, II, III, VR, VL, VF, V5, V6
6	Sinus	I, VL	II, III, VF	I, VL, V6
7	Sinus	I, VL, V6	I, II, III, VR, VF	None
8	Sinus	II, III, VF, V4–V6	None	None
9	Sinus	II, III, VF, V5, V6	I, II, VR	None
10	Sinus	III, VF	II	III, VF

and leads VR and VF. Abnormal Q waves were present in five cases, in two in leads I and VL and in three in leads III and VF. Abnormal T waves were present in five of the patients. Although the tracings suggested left ventricular dominance in some instances, and right ventricular dominance in others, there were always additional features indicating more complex myocardial abnormality (Plate 16, Fig. 3; Plate 18, Fig. 7; Plate 20, Fig. 11; Plate 21, Fig. 13).

4. *Cardiac catheterization* was done in two of the patients (Cases 1 and 5) by Dr. J. M. Bishop. Both had had symptoms for many years. There was no evidence of an intracardiac shunt in either case, and both had normal arterial oxygen saturation at rest and on exercise. The right heart pressure was elevated in both cases: in Case 1 the mean right auricular pressure was 6 mm. Hg at rest, rising to 24 mm. Hg on exercise, and the right ventricular pressure 58/2 mm. Hg at rest; in Case 5 the mean pulmonary wedge pressure was 17 mm. Hg at rest, rising to 40 mm. Hg on exercise. The cardiac output in Case 1 was 5·24 litres per minute at rest, rising to 9·00 litres per minute on exercise, and in Case 5 4·75 litres per minute at rest, rising to only 4·99 litres per minute on exercise.

5. *Angiocardiography* was carried out in two patients (Cases 1 and 5) by Dr. F. H. Howarth. In Case 5 it was unsuccessful owing to a fault in the catheter, and it was considered unjustifiable to repeat the procedure because of the slight risks involved. In Case 1 the heart chambers were shown to be normal in size and position, and there was no evidence of an intracardiac shunt. The pulmonary infundibulum, pulmonary valve, and pulmonary arteries appeared normal, as did the aortic valve. There were no signs of hypertrophy of the right ventricle, but the wall of the left ventricle appeared to be thickened (Plate 16, Fig. 4).

6. *Other investigations and observations.* None of the patients showed any pyrexia during the period in which they have been under observation, and the erythrocyte sedimentation rate, where estimated, was normal except in Case 1; in this patient it was just outside the normal range at 23 mm. in one hour

TABLE IV

Evidence of Toxoplasmosis

(Complement fixation and dye tests done by Dr. J. K. A. Beverley)

Case number	*Skull X-rays*	*Complement fixation test*	*Dye test (titre)*
1	Normal	Negative	1 in 68
5	Normal	Negative	1 in 60
	..	Negative*	1 in 30*
6	Normal	Negative	1 in 5
7	Not done	Negative	Negative

* Second examination carried out two months after the first.

(Wintrobe). None of the patients were anaemic, and their white-cell counts were normal. Pulmonary function tests were done in two patients. In Case 1 the vital capacity, timed vital capacity, maximum breathing capacity, and expiratory flow rates were normal; in Case 5 the vital capacity was normal, but the timed vital capacity, maximum breathing capacity, and expiratory flow rates were all slightly reduced. Search for evidence of toxoplasmosis was made in four of the patients, and the results are summarized in Table IV, from which it will be seen that the skull radiographs showed no abnormality and the complement fixation tests were negative, but the dye test was positive in three of the four patients. This last finding is probably without significance. Blood-group studies in five members of the family showed nothing to suggest that the cardiomyopathy was linked to blood group or to Rh phenotype or genotype.

7. *Pathological findings.* Autopsies were carried out in only two of the patients (Cases 2 and 4). In Case 4 the post-mortem examination was carried out at the instruction of H.M. Coroner, and the records merely state that the heart showed marked myocardial and fatty degeneration. In Case 2 we are greatly indebted to Dr. A. G. Marshall for most careful and detailed macroscopic and histological examination. The heart was of globular shape, and weighed 335 g., of which the left ventricle comprised 170 g. and the right ventricle 65 g. The valves, coronary arteries, aorta, and pulmonary arteries were normal, and all foramina, including the ductus, were closed. The ventricles appeared rather small, and the auricles large and somewhat hypertrophied. The striking naked-eye feature, however, was the myocardium, which was pale and firm. Microscopic examination (Plate 17) showed widespread hypertrophy of myofibrils, and patchy atrophy and fibrosis. There were no Aschoff bodies, and the intramyocardial arteries and arterioles appeared normal. A mild degree of endocardial fibro-elastosis of the left auricle was evident.

Discussion

There can be no doubt about the existence of familial cardiomyopathy as a clinical entity. The observed presence of such an unusual form of heart disease in 10 members of this family, and the fact that six others are almost certainly affected by the condition, could not possibly be accounted for by chance. Moreover, similar families have been reported in the Case Records of the Massachusetts General Hospital (1942), and by Addarii, Martini, Mahaim, and Winston (1946), Evans (1949), Davies (1952), Blanshard (1953), Paulley, Jones, Green, and Kane (1954, 1956), Gaunt and Lecutier (1956), Campbell and Turner-Warwick (1956), and Brigden (1957). The two major enigmas are the factors responsible for the familial incidence and the exact nature of the pathological process. With regard to the former, it will be seen from Fig. 1 that in the family here reported, although male and female members are affected, transmission appears to have occurred only through the female. The same is evident in all the other families described. Although, if more complete information regarding the various families were available, this observation might be proved fallacious, it is certainly not attributable to failure of the male patients to survive to procreative age. From Fig. 1 it will also be seen that the condition appears to be passed on only to the children of the affected women, the progeny of unaffected women being normal. The same pattern is evident in the other recorded families. Birth rank is clearly not a factor, as in the family here reported and in the other families described neither the oldest nor the youngest members showed any special liability to the condition.

None of the members of the family here reported showed any neurological abnormality, but Kiloh and Nevin (1951) described a family in which some members had pseudohypertrophic muscular dystrophy and some cardiomyopathy, and one male subject had both conditions. Storstein and Austarheim (1955) also reported a male patient with progressive muscular dystrophy who died from cardiomyopathy. Zatuchni, Aegerter, Molthan, and Shuman (1951) described a similar case, and stated that 94 of 292 patients with progressive muscular dystrophy previously reported showed evidence of cardiovascular abnormality. Roth (1948) reported a family in which Freidrich's ataxia with peroneal muscular atrophy affected some members and others suffered from heart disease. While these observations are of great interest, they do not provide any information as to the factors responsible for the hereditary and familial incidence, and indeed it is by no means certain that the heart disease associated with the heredo-familial muscular dystrophies and ataxias is the same as that which has been described as familial cardiomyopathy. Furthermore, it appears probable that there is some diversity even in the cardiomyopathies of familial incidence. In most of the families previously reported (Case Records of the Massachusetts General Hospital, 1942; Addarii, Martini, Mahaim, and Winston, 1946; Evans, 1949; Paulley, Jones, Green, and Kane, 1954, 1956; Gaunt and Lecutier, 1956; Campbell and Turner-Warwick, 1956)

gross conduction defects have been a striking feature, but they were not seen in any of the members of the family here described.

Paulley, Jones, Green, and Kane (1954, 1956) have suggested that familial cardiomyopathy may be due to myocardial toxoplasmosis, and such an aetiological explanation, though attractive and not improbable, cannot be regarded as proven. Toxoplasma has been found on histological examination of the heart in a fatal case of toxoplasmosis (Pinkerton and Weinman, 1940), and Bengtsson (1950) reported a non-fatal case of toxoplasmosis in an adult in whom dyspnoea, anginal pains, and electrocardiographic changes were a feature. But the toxoplasma protozoon has not been seen in the hearts of any patients who died from familial cardiomyopathy, and the case for toxoplasmosis rests largely on the presence of cerebral lesions in some cases and on the finding of positive dye and complement-fixation tests. The latter form of evidence, though highly suggestive, is difficult to interpret, as positive dye tests are found in a substantial proportion of normal persons, and other common conditions, such as trichomonas infection, can give rise to positive complement fixation tests (Beverley, 1959; Paulley, 1959). In the family here described no evidence of toxoplasmosis was found (Table IV).

Blood-group studies have not been reported in previously described families but, as has already been stated, the affected members of the family we have studied were of differing blood groups, Rh phenotype and genotype.

With regard to the nature of the pathological process in the heart in cases of familial cardiomyopathy, the most striking feature of all fatal cases reported has been hypertrophy and fibrosis of the myocardium and normal coronary arteries, and these were certainly the findings in Case 2 of this family. During life, however, anginal pain may be present (Cases 2, 5, and 6; Blanshard, 1953; Paulley, Jones, Green, and Kane, 1956; Campbell and Turner-Warwick, 1956), and the electrocardiogram commonly shows big P waves, dominance of one or other ventricle, and ischaemic changes or gross conduction defects. It seems, therefore, that the essential pathology is a hypertrophy of myofibrils which outstrip their blood supply, but the precise cause of the hypertrophy remains unexplained. It is certainly not the result of hypertension or valvular disease, or any of the other recognized causes of cardiac hypertrophy.

Except that it may bring life to an end before childbearing years are reached (Case 4), or before the menopause (Case 2), the condition does not appear to prevent childbearing; one patient (Case 16) had 11 children, and another (Case 3) a family of eight; but three of the patients (Cases 1, 2, and 6) were much worse during pregnancy, and in Case 2 pregnancy precipitated a protracted episode of cardiac failure. It seems probable that this temporary increase in the degree of disability was wholly attributable to the haemodynamic changes associated with pregnancy, but there are many points of similarity between familial and puerperal cardiomyopathy, and some non-fatal cases of puerperal cardiomyopathy do not return to normality (Brigden, 1957; Meadows, 1957). It may therefore be that some aetiological factors are common to both conditions.

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APPENDIX

Case 1. A married woman of 23 was referred by her general practitioner in August 1957 for an opinion as to the advisability of further pregnancy. She gave no history of rheumatic fever, chorea, or other illness, but had been breathless on exertion since childhood, and her dyspnoea had been very much worse during her only pregnancy, which had come to term in January 1955. She had no symptoms apart from dyspnoea on exertion, and the only abnormal physical signs were loud gallop rhythm and a grade 2 pulmonary systolic murmur. The gallop rhythm disappeared after she had rested for a few minutes and become quite calm, only to reappear on the slightest exertion or excitement. There was no clinical enlargement of the heart, the blood-pressure was 140/80, and there was normal pulsation in the femoral and pedal arteries. The central nervous system was normal, the chest was clear, there was nothing to be felt in the abdomen, and there were no abnormal constituents in the urine. Radiology showed no cardiac enlargement (cardio-thoracic ratio 48 per cent.), but the heart was of 'mitral' shape (Plate 16, Fig. 2), and the left auricle appeared to be enlarged, the outflow tract of the right ventricle prominent, and the aorta hypoplastic. The electrocardiogram (Plate 16, Fig. 3) showed left ventricular preponderance and prominent P waves in leads II and VF. The blood count was normal, and the erythrocyte sedimentation rate was 23 mm. in one hour (Wintrobe). Though the aetiology and anatomical nature of the cardiac disease appeared obscure, it was not considered justifiable at that time to carry investigation further, and she was kept under out-patient surveillance for the next two years, during which there was no change in the symptoms, the physical signs, the radiological appearances, or the electrocardiogram. In the summer of 1959 she was admitted to hospital in the hope that cardiac catheterization and angiocardiography would provide a precise diagnosis. Cardiac catheterization (Dr. J. M. Bishop) showed a right auricular pressure of 6 mm. Hg and a right ventricular pressure of 58/2 mm. Hg at rest; on exercise the right auricular pressure rose to 24 mm. Hg. There was no shunt. It was impossible to advance the catheter beyond the right ventricle. The cardiac output at rest was 5·24 litres per minute, rising on exercise to 9·0 litres per minute. The arterial oxygen saturation at rest and on exercise was 98·6 per cent. The vital capacity, timed vital capacity, maximum expiratory flow rate, and maximum breathing capacity were normal. Angiocardiography (Dr. F. H. Howarth) showed normal cardiac chambers, no shunt, normal pulmonary and aortic valves, and a normal aorta and pulmonary arteries, the only abnormality revealed being a thickening of the wall of the left ventricle (Plate 16, Fig. 4). An exact diagnosis seemed no nearer until the patient told us of her sister's death from heart failure in October

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Case 1. A married woman of 23 was referred by her general practitioner in August 1957 for an opinion as to the advisability of further pregnancy. She gave no history of rheumatic fever, chorea, or other illness, but had been breathless on exertion since childhood, and her dyspnoea had been very much worse during her only pregnancy, which had come to term in January 1955. She had no symptoms apart from dyspnoea on exertion, and the only abnormal physical signs were loud gallop rhythm and a grade 2 pulmonary systolic murmur. The gallop rhythm disappeared after she had rested for a few minutes and become quite calm, only to reappear on the slightest exertion or excitement. There was no clinical enlargement of the heart, the blood-pressure was 140/80, and there was normal pulsation in the femoral and pedal arteries. The central nervous system was normal, the chest was clear, there was nothing to be felt in the abdomen, and there were no abnormal constituents in the urine. Radiology showed no cardiac enlargement (cardio-thoracic ratio 48 per cent.), but the heart was of 'mitral' shape (Plate 16, Fig. 2), and the left auricle appeared to be enlarged, the outflow tract of the right ventricle prominent, and the aorta hypoplastic. The electrocardiogram (Plate 16, Fig. 3) showed left ventricular preponderance and prominent P waves in leads II and VF. The blood count was normal, and the erythrocyte sedimentation rate was 23 mm. in one hour (Wintrobe). Though the aetiology and anatomical nature of the cardiac disease appeared obscure, it was not considered justifiable at that time to carry investigation further, and she was kept under out-patient surveillance for the next two years, during which there was no change in the symptoms, the physical signs, the radiological appearances, or the electrocardiogram. In the summer of 1959 she was admitted to hospital in the hope that cardiac catheterization and angiocardiography would provide a precise diagnosis. Cardiac catheterization (Dr. J. M. Bishop) showed a right auricular pressure of 6 mm. Hg and a right ventricular pressure of 58/2 mm. Hg at rest; on exercise the right auricular pressure rose to 24 mm. Hg. There was no shunt. It was impossible to advance the catheter beyond the right ventricle. The cardiac output at rest was 5·24 litres per minute, rising on exercise to 9·0 litres per minute. The arterial oxygen saturation at rest and on exercise was 98·6 per cent. The vital capacity, timed vital capacity, maximum expiratory flow rate, and maximum breathing capacity were normal. Angiocardiography (Dr. F. H. Howarth) showed normal cardiac chambers, no shunt, normal pulmonary and aortic valves, and a normal aorta and pulmonary arteries, the only abnormality revealed being a thickening of the wall of the left ventricle (Plate 16, Fig. 4). An exact diagnosis seemed no nearer until the patient told us of her sister's death from heart failure in October

1958 at the age of 27, and of her mother's death in August 1958, also from heart failure. This aroused our suspicions of familial cardiomyopathy, which were fully confirmed by the case notes of the sister (Case 2) and her mother (Case 3), which were kindly placed at our disposal by Dr. J. H. Sheldon and Dr. E. J. Blair, and by further inquiry into her family history. The patient has been kept under observation until the time of writing, and her condition has not materially changed.

Case 2. An elder sister of our first patient was breathless on exertion from childhood. At the age of 16 she had a tuberculous pleurisy, but there was no history of rheumatic fever, chorea, or other significant illness. When 17 years old she was admitted to the Royal Hospital, Wolverhampton, under the care of Dr. J. H. Sheldon, for investigation of her dyspnoea; at this time a systolic murmur was audible all over the precordium, and she was thought to have a patent interventricular septum. She got through her first pregnancy, at the age of 21, uneventfully, but during her second pregnancy four years later she developed severe congestive cardiac failure, and was in New Cross Hospital, Wolverhampton, for five months before premature delivery at 32 weeks. Thereafter her cardiac failure rapidly disappeared, but exertion and emotional stimulus provoked pain in the chest and back, which radiated to the neck and was accompanied by paraesthesia in both arms. She was again seen by Dr. Sheldon, who could then hear no murmurs, but noticed that the radiological appearances of the heart suggested mitral stenosis. When aged 27 she again had severe congestive cardiac failure, and was readmitted to the Royal Hospital, Wolverhampton, under the care of Dr. Sheldon in September 1958 with orthopnoea, sacral and leg oedema, haemoptysis, and haematuria. The pulse was irregular, and electrocardiography showed the irregularity to be due to flutter. The blood-pressure was 115/95. No murmurs could be heard, but the chest radiograph showed a large heart (cardio-thoracic ratio 59 per cent.) of 'mitral' shape, consolidation in the right upper zone, and calcified right hilar and paratracheal glands. There was no response to treatment, and the patient died 19 days later. At autopsy (carried out by Dr. A. G. Marshall) the heart weighed 335 g., of which the right ventricle contributed 65 g. and the left 170 g. The auricles were hypertrophied and appeared large, while the ventricles were rather small, the whole heart having a globular shape. The valves and coronary arteries were normal, and all foramina, including the ductus, were closed; the aorta was normal, as were the pulmonary arteries, except for one or two tiny patches of atheroma. The myocardium appeared pale and firm. The liver showed coarse nodular hyperplasia and fibrosis. There were numerous pulmonary infarcts, old pleural adhesions on the right side, and caseating tuberculous glands at the apex of the pericardium. The kidneys and spleen were congested, and there was one renal infarct, but the remaining organs were macroscopically normal. Histological examination of the myocardium showed widespread hypertrophy of myofibrils, and patchy atrophy and fibrosis (Plate 17). There were no Aschoff bodies, and the arteries and arterioles showed no abnormal features. Histology confirmed the presence of caseating tuberculosis in the mediastinal lymph-nodes and cardiac cirrhosis in the liver, but there were no other significant findings.

Case 3. A woman aged 57, the mother of the two preceding patients, was admitted to New Cross Hospital, Wolverhampton, in August 1958 under the care of Dr. E. J. Blair, with a two-day history of anorexia, vomiting, and abdominal pain. There had been no significant previous illness and no other symptoms, and she had had eight children without difficulty. There was slight tenderness in the right upper quadrant of the abdomen, but this and the

alimentary symptoms rapidly subsided, and it was thought that they were possibly embolic in origin, as she was noted to have auricular fibrillation. There were no heart murmurs, and the blood-pressure was 110/80. A chest radiograph showed a heart of 'mitral' contour, but no enlargement; screening suggested right ventricular enlargement, but the left auricle appeared normal. The electrocardiogram showed auricular fibrillation, and inverted T waves in leads I, II, III, VL, VF, and V3 to V7. She was discharged on treatment with digoxin, and more detailed cardiological investigation was under consideration when, six weeks later, a left femoral embolus necessitated her readmission as an emergency. A mid-thigh amputation was performed, after which she developed congestive cardiac failure, which proved unresponsive to treatment, and she died five weeks after operation. There was no autopsy.

Case 4. A younger sister of patient No. 1, and a daughter of patient No. 3, had been short of breath on exertion for many years, and died suddenly at the age of 17 while cycling to hospital for consultation. At the coroner's post-mortem examination (carried out by Dr. A. Byrne-Quinn) marked myocardial and fatty degeneration of the heart was found, and death was certified as being due to cardiac failure as a result of chronic myocarditis. All other organs were normal.

Case 5. A woman aged 37, the eldest sister of patient No. 1 and a daughter of patient No. 3, had an attack of right-sided pleurisy at the age of 19, and was kept in bed for 16 weeks. Ever since this illness she has had shortness of breath on exertion, and has been subject to attacks of palpitation, which sometimes appear to be provoked by exertion or excitement, but at other times occur without obvious cause. During the past two years she has had pain in the left arm as well as dyspnoea on exertion, and the pain often takes as long as an hour to subside. At the age of 22 she had four attacks of unconsciousness which were diagnosed as 'heart attacks', but from her description of them it seems probable that they were episodes of major epilepsy. She has had no children. She has been observed for a period of six months, and during this time there has been no evidence of cardiac failure. She has a pigeon-chest deformity. A grade 2 systolic murmur is constantly audible just inside the mitral area, and gallop rhythm is sometimes present. The blood-pressure is usually of the order of 110/70. An aberrant brachial artery is present on the left side. Otherwise there are no objective cardiovascular abnormalities, and the central nervous system, lungs, abdomen, and urine are normal. The chest radiograph (Plate 18, Fig. 6) shows moderate cardiac enlargement (cardio-thoracic ratio 53 per cent.), and screening indicates enlargement of the right ventricle and left auricle and prominence of the pulmonary conus, while the aortic knuckle appears a little smaller than normal. The electrocardiogram, however (Plate 18, Fig. 7), suggests left ventricular hypertrophy and ischaemia. The prominent P waves in leads I, II, III, VR, and VF, and their bifid pattern in leads III and V2 to V6, are a striking feature. Cardiac catheterization (Dr. J. M. Bishop) showed no evidence of an intracardiac shunt. The cardiac output at rest was 4·75 litres per minute, rising to only 4·99 litres per minute on exercise. The mean pulmonary artery and pulmonary wedge pressures were 20 mm. Hg and 17 mm. Hg respectively, rising on exercise to 47 mm. Hg and 40 mm. Hg. The arterial oxygen saturation was 98 per cent. Pulmonary function studies showed a normal vital capacity, but slight diminution in the maximum breathing capacity, timed vital capacity, and maximum expiratory flow rate. Angiocardiography was attempted but was unsuccessful, and it was not thought justifiable to repeat the investigation. The

blood count was normal, and the erythrocyte sedimentation rate was 5 mm. in one hour (Wintrobe). No treatment has been offered other than nitroglycerine for the relief of the pain in the left arm, a measure which appears to be reasonably effective.

Case 6. A woman aged 30, an elder sister of patient No. 1 and a daughter of patient No. 3, has been increasingly dyspnoeic on exertion since the age of 19, and has been troubled by palpitation since the age of 21. For the past four years she has been blue on exertion, and for 12 months exertion has provoked pain in the left pectoral region radiating to the left arm, the neck, and the lower jaw, and often persisting for two hours or more. There has been a striking variability in her exercise tolerance: sometimes she is able to lead a reasonably normal life without undue distress, while at other times mounting one flight of stairs is sufficient to provoke severe dyspnoea and pain. She gives no history of rheumatism or other illness, and has three children aged seven, four, and two years (Cases 7, 8, and 9). During her first pregnancy she was diagnosed as having a 'leaking valve' and had to 'take things easily', but she seems to have got through the pregnancy and labour without undue difficulty. During the second and third pregnancies, however, her dyspnoea was much worse and severely restricted her activity. On examination she is slightly cyanotic, but there is no dyspnoea at rest, and no evidence of cardiac failure. A grade 2 systolic murmur is audible, loudest in the pulmonary area, and the first sound is split in the mitral and tricuspid areas, but no gallop rhythm has ever been detected even after exercise. Occasional bursts of regular tachycardia, at a rate of 140 per minute, have been observed during examination. The blood-pressure is 110/70, and the peripheral pulses are all present and normal. There are no neurological abnormalities, and the lungs, abdomen, and urine are normal. The chest radiograph (Plate 19, Fig. 8) shows slight cardiac enlargement (cardio-thoracic ratio 51 per cent.) and a rather straight left cardiac border, while screening suggests diffuse enlargement rather than the involvement of any particular chamber. The electrocardiogram (Plate 19, Fig. 9) shows Q waves in leads I and VL, flat T waves in leads I, VL, and V6, and large P waves in leads II, III, and VF. The blood count is normal. There has been no significant change in the symptoms, physical signs, chest radiograph, or electrocardiogram during the six months in which she has been under observation.

Case 7. A girl aged seven, the elder daughter of patient No. 6 and a grandchild of patient No. 3, has had no significant illness, and has normal exercise tolerance and no symptoms. There are no objective abnormalities except in the cardiovascular system. A grade 2 systolic murmur is audible, loudest in the mitral area, and the first sound is split in the pulmonary and tricuspid areas. The blood-pressure is 90/60, and all peripheral pulses are present and normal. The chest radiograph (Plate 20, Fig. 10) shows an enlarged heart (cardio-thoracic ratio 52 per cent.) with a straight left border, and screening indicates enlargement of both ventricles. The electrocardiogram (Plate 20, Fig. 11) shows Q waves in leads I, VL, and V6, and big pointed P waves in leads I, II, III, VR, and VF. There has been no change in the physical signs, X-ray appearances, or electrocardiogram during the six months she has been under observation.

Case 8. A boy aged four, the son of patient No. 6 and grandson of patient No. 3, has had no illness apart from otitis media, and has normal exercise tolerance and no symptoms. A grade 3 pulmonary systolic murmur is audible, but no thrill can be detected. The blood-pressure is 80/55. All peripheral pulses

are present and normal. The lungs, abdomen, urine, and central nervous system show no abnormality. The chest radiograph and screening show no cardiac enlargement, but a straight left cardiac border. The electrocardiogram suggests right ventricular dominance, and shows Q waves in leads II, III, VF, and V4 to V6.

Case 9. A girl aged two years, the younger daughter of patient No. 6, and a granddaughter of patient No. 3, appears quite healthy, but a cardiac murmur was detected at birth. Now she has a grade 3 systolic murmur, loudest over the base of the heart. No thrill can be felt. The chest radiograph (Plate 21, Fig. 12) shows gross cardiac enlargement (cardio-thoracic ratio 58 per cent.), the shape suggesting left ventricular enlargement, but the electrocardiogram (Plate 21, Fig. 13) suggests right ventricular preponderance, and shows Q waves in leads II, III, VF, V5, and V6, and prominent pointed P waves in leads I, II, and VR.

Case 10. A girl aged four, the only child of patient No. 1 and a granddaughter of patient No. 3, has had no significant illness and appears quite healthy and normal; there are no abnormalities to be found in the cardiovascular system or elsewhere on ordinary physical examination. The chest radiograph (Plate 21, Fig. 14), however, shows cardiac enlargement (cardio-thoracic ratio 57 per cent.) and a 'mitralized' left border, and screening indicates a diffuse enlargement rather than the involvement of any particular chamber. The electrocardiogram shows Q waves and abnormal T waves in leads III and VF, and prominent pointed P waves in lead II.

Case 11. A brother of patient No. 3 and a maternal uncle of patients 1, 2, 4, 5, and 6, died suddenly while cycling to work at the age of 36. A coroner's inquest was held, and death was stated to be due to heart failure.

Case 12. A brother of patients 3 and 11 was serving in the Royal Navy, and while returning to England aboard ship died suddenly from heart failure at the age of 40.

Case 13. A sister of patients 3, 11, and 12 has had 'heart trouble' for many years, but has had four children, and is still alive at the age of 37.

Case 14. A sister of patients 3, 11, 12, and 13 is known to have 'heart trouble', but is alive at the age of 35, and is known to have had children, but the size of her family is not known.

Case 15. A sister of patients 3, 11, 12, 13, and 14 was born with no fingers on the left hand. She is known to have slight heart trouble. Now aged 26, she has had two children.

Case 16. The mother of patients 3, 11, 12, 13, 14, and 15, and grandmother of patients 1, 2, 4, 5, and 6, always had a bad heart, and died at the age of 54 after being in bed with heart failure for three months. She had 11 children, of whom three (Cases 3, 11, and 12) have died from heart disease, and three others (Cases 13, 14, and 15) are known to have heart disease. Her eldest son died at the age of 40 from kidney trouble, but the remaining four children are, as far as is known, in good health.

Summary

A family is described in which 10 members are suffering, or have died, from cardiomyopathy, and six others are probably similarly affected. Of the 16 three have died suddenly, and three have died from congestive heart failure. Ten are still alive, six adults with some degree of cardiac disability, and four children who are without symptoms. The clinical, radiological, electrocardiographic, and pathological findings are described, and the aetiology of the condition is discussed.

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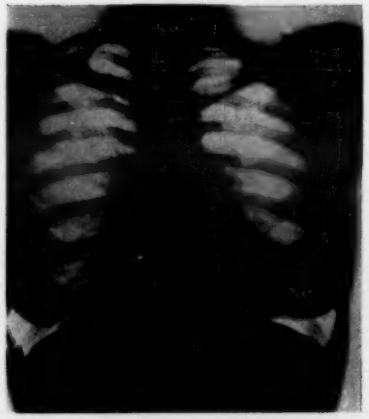


FIG. 2. Case 1. 'Mitral' configuration of heart but no enlargement

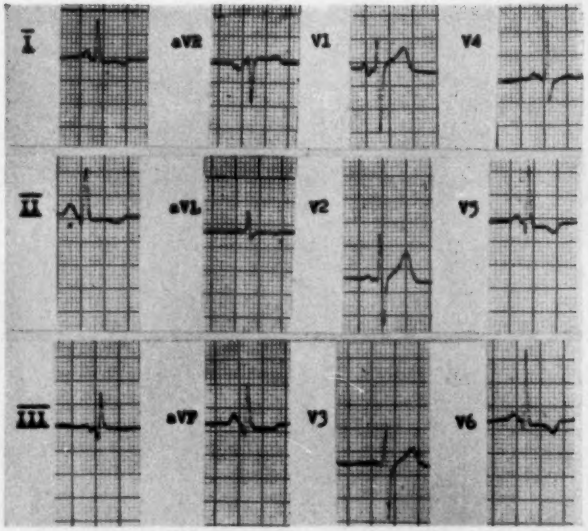


FIG. 3. Case 1. Left ventricular preponderance with large P waves in leads II and VF

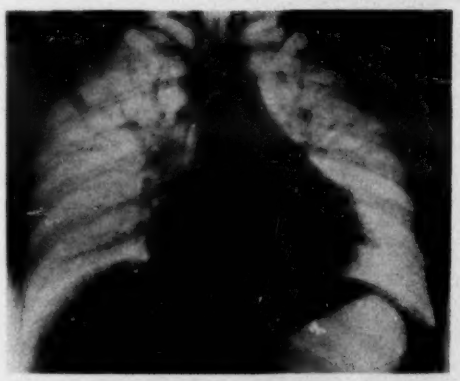
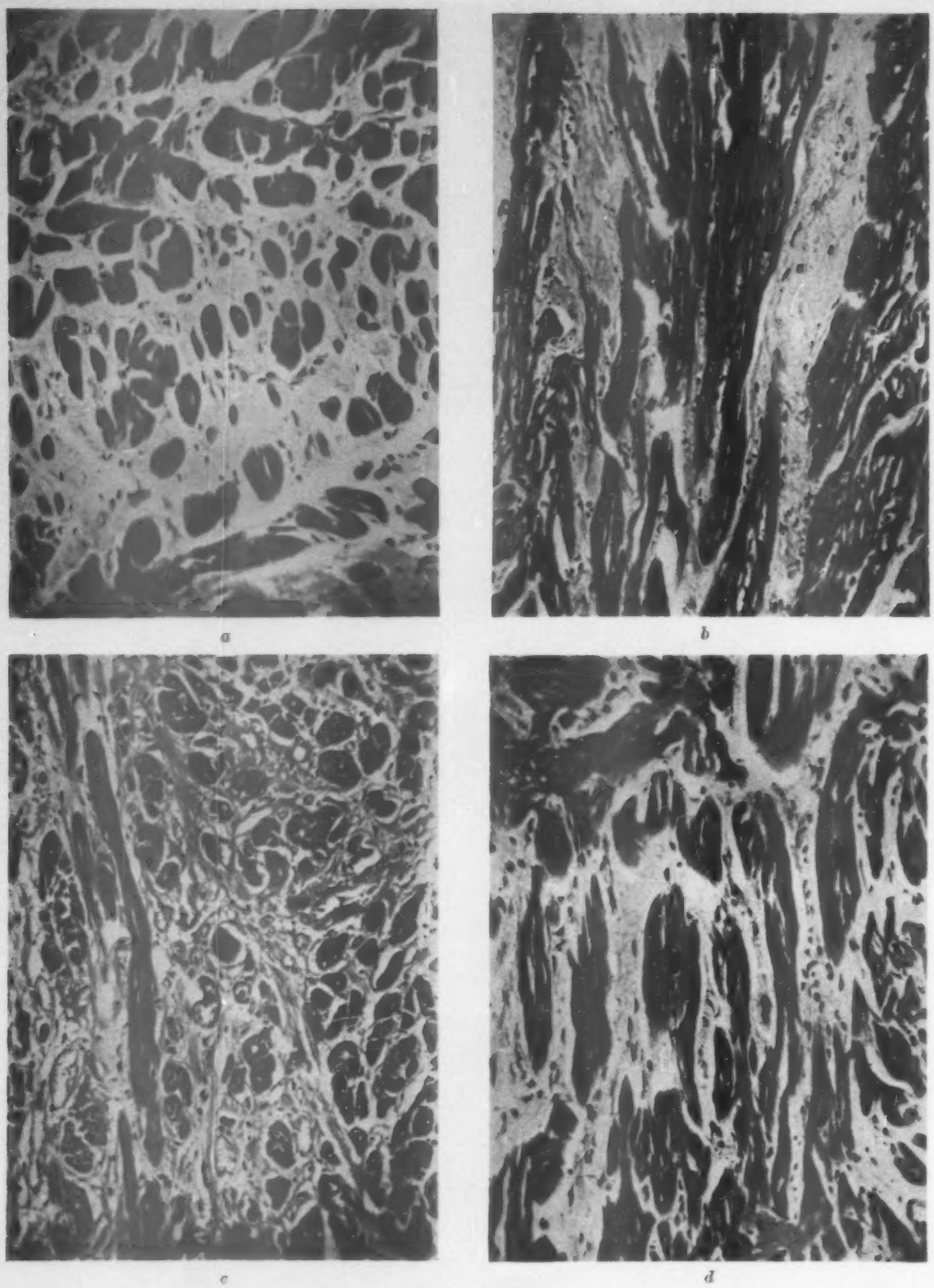


FIG. 4. Case 1. Angiocardiogram showing increased thickness of the left ventricular wall



a *b*

c *d*

FIG. 5 (*a*, *b*, *c*, *d*). Case 2. Myocardium showing widespread hypertrophy of myofibrils with patchy atrophy and fibrosis. No sign of Aschoff bodies

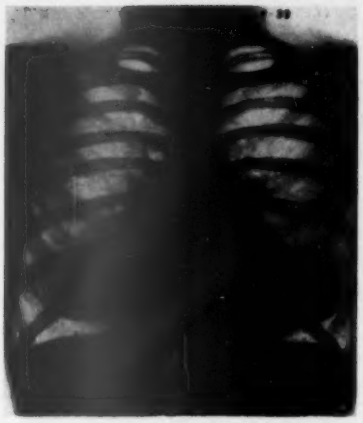


FIG. 6. Case 5. Globular heart shadow

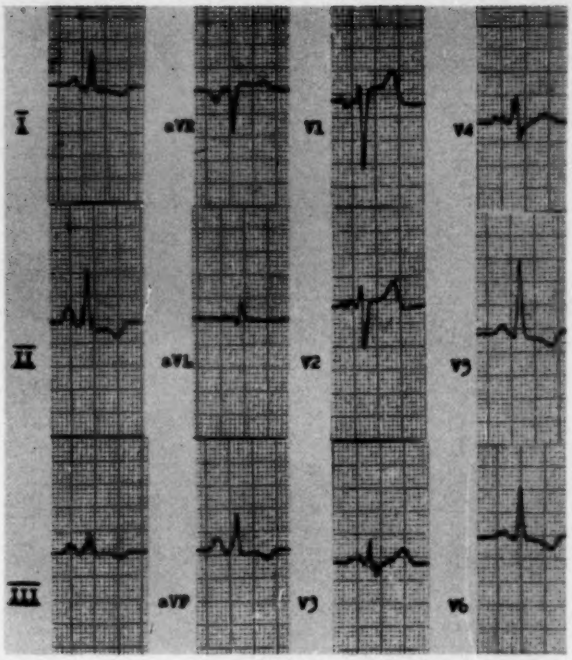


FIG. 7. Case 5. Left ventricular preponderance with abnormal P waves in almost all leads

FIG. 8. Case 6. Enlarged heart with a rather straight left border

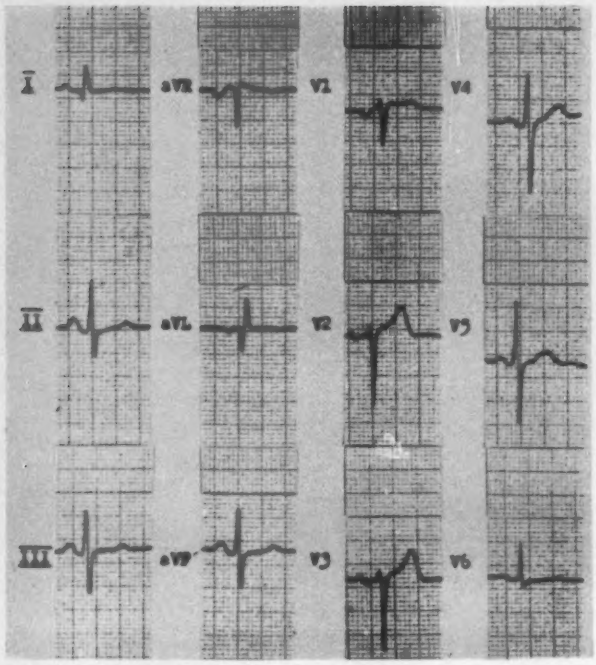


FIG. 9. Case 6. Q waves in leads I and VL. Flat T waves in leads I, VL, and V6, and large P waves in leads II, III, and VF

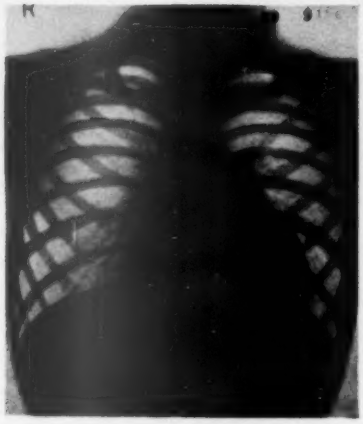


FIG. 10. Case. 7. **Enlarged heart with a rather straight left border**

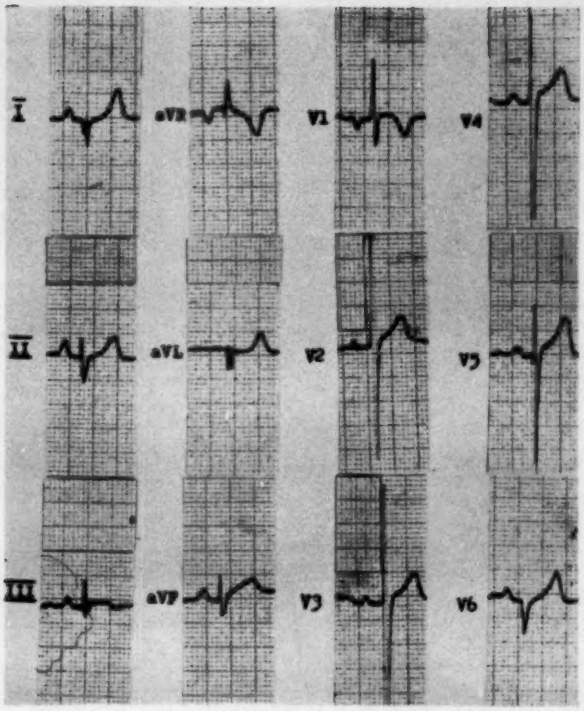


FIG. 11. Case 7. **Q waves in leads I, VL, and V6. Big pointed P waves in all standard leads and in leads VR and VF**

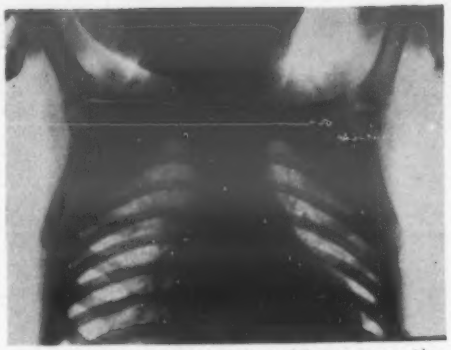


FIG. 12. Case 9. Much enlarged heart suggesting left ventricular hypertrophy

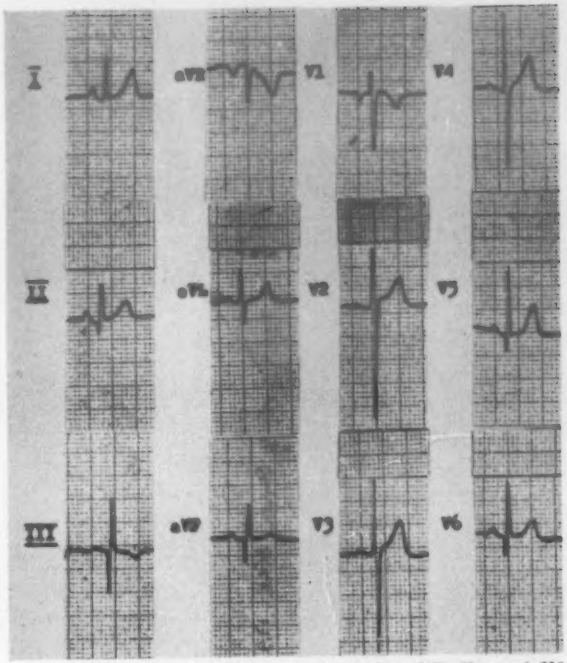


FIG. 13. Case 9. Q waves in leads II, III, VF, V5, and V6. Prominent pointed P waves in leads I, II, and VR

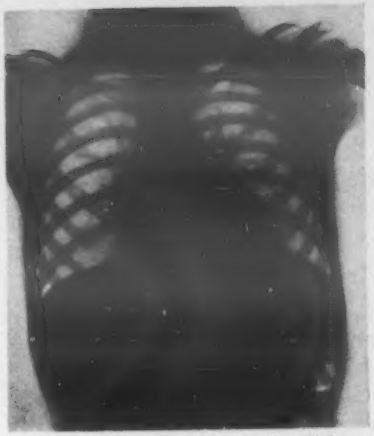
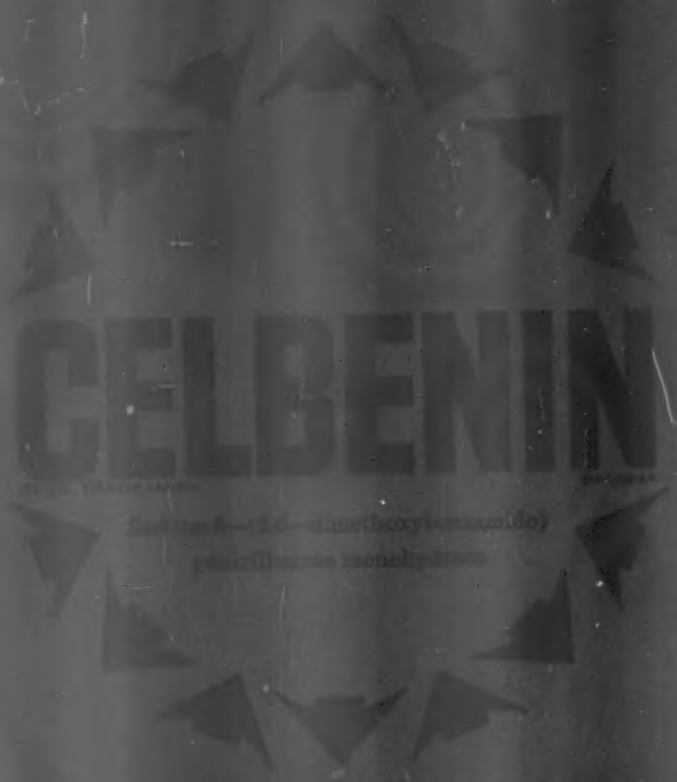


FIG. 14. Case 10. Much enlarged heart with a 'mitralized' left border



Sodium 6-(2,6-dimethoxybenzamido) penicillinate monohydrate

"A new penicillin has been prepared which is active against the usual penicillin-sensitive microorganisms and yet resists staphylococcal penicillinase. This is a major event in chemotherapy. From the information given in the British Medical Journal last week and in the three papers appearing in our present issue there is good reason to hope that the new BRL 1241 ('Celbenin', Beecham Research Laboratories) will be a means of controlling the staphylococcal infections which have plagued hospitals throughout the world during the past ten years."

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Seven papers recording work on Celbenin appeared in the British Medical Journal of September 3rd, 1960, on pages 637, 690, 694, 700, 705, 709 and 716; three in the Lancet of September 17th, 1960, on pages 564, 568 and 569.

CELBENIN is a product of Beecham Research at BEECHAM RESEARCH LABORATORIES Brockham Park, Betchworth, England.